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Sensory-Motor Integration in the Medial Medulla

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Abstract: The rostromedial medulla, including the nucleus gigantocellularis (NGC) and magnocellularis (NMC), plays a role as a relay nucleus for both the sensory and motor systems. The NGC/NMC is important in the modulation of somatic and visceral activities. Electrophysiological and pharmacological studies have shown that the NGC/NMC is involved in nociception, locomotion, regulation of basal muscle tone, sleep, as well as cardiovascular and pulmonary activities. Pharmacological and electrical stimulation of the NGC/NMC can produce opposite effects on physiological functions: analgesia or hyperalgesia, and suppression or facilitation of motor activity, depending on the subgroups of neurons activated and the states of the sleep-wake cycle at the time of stimulation. Sensory inputs including noxious and innocuous stimuli converge on the NGC/NMC. The NGC/NMC also plays a role as a relay nucleus, which sends sensory information to the higher centers. The NGC/NMC receives projections from the supra-bulbar motor facilitatory and inhibitory areas, and plays an important role in the regulation of motor activity. Pharmacologically, neurons in the NGC/NMC contribute to opioid, glutamate, GABA, acetylcholine, dopamine, substance P, neurotensin, hypocretin (orexin), and cannabinoid mediated sensory and motor activities, as well as cardiovascular and pulmonary functions. In this review, we will discuss the neuronal morphology, physiological functions and pharmacological characterization of the rostromedial medulla. We will consider the evidence that dysfunction of the NGC/NMC is a factor in a number of neurological diseases, including Parkinson's disease, restless legs syndrome, periodic leg movement, REM sleep behavior disorder, amyotrophic lateral sclerosis and narcolepsy.

Key Words: Opioid, glutamate, GABA, glycine, dopamine, acetylcholine, serotonin, nociception, Parkinsonism, periodic leg movement, myoclonus, narcolepsy, REM sleep behavior disorder, restless legs syndrome.

INTRODUNTION

The medullary reticular formation is traditionally segregated into the medial somatic- and lateral visceral-related areas. However, somatic and autonomic activities are well coordinated. For example, cardiovascular-respiratory changes are correlated with somatic sensory-motor activity during exercise. Coordination of somatic and autonomic activity can result from interconnections between somatic and autonomic control structures, as well as interactions within nuclei, which are involved in both somatic and autonomic activities. The rostromedial medulla (RMM) is one of the areas of the central nervous system (CNS) that is involved in both somatic and autonomic regulation. However, the RMM has traditionally been considered as a somatic nociceptive and a motor control area. The autonomic role of the RMM has received little attention, although Bach [22] demonstrated that the activation of RMM causes changes in cardiovascular and respiratory activity, as well as the facilitation and inhibition of somatic motor activity in 1952. Therefore, we will discuss the functional aspects of RMM in the modulation of both somatic and autonomic systems in this review. Section 1 will focus on the morphology of the RMM, and the anatomical link between RMM and the other areas of the CNS. Section 2 will discuss physiological data on the role of the RMM in sensory-motor integration and autonomic modulation. The effects of sensory stimuli on RMM neuronal activity and of neuronal activity in the RMM on sensory processing and motor outputs will also be discussed. Section 3 will focus on pharmacological studies of the effects of activation and inactivation of RMM effect on somatic sensory and motor systems, as well as autonomic system. Section 4 will describe the involvement of RMM in neurological disorders.

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1. ANATOMICAL STUDIES OF THE ROSTROMEDIAL MEDULLA

1.1. Terminology of the Rostromedial Medulla

The RMM can be divided anatomically into 2 regions. The nucleus gigantocellularis (NGC), which contains giant neurons, in the dorsal portion, and the nucleus magnocellularis (NMC), which has small to large sized neuron, in the ventral portion of the RMM (Fig. 1). Terminology used for the ventral portion of the RMM has varied as a function of species and author. NGC alpha (NGCα) in the rostroventral and NGC ventralis (NGCv) in the caudoventral RMM has been used in the rodent [362]. In the cat, NGC is used to represent the entire area of the RMM according to Snider and Niemer [440] and Taber [453], whereas NGC and NMC are used to designate the dorsal and ventral RMM, respectively, by Berman [33].

Though NGC and NMC (NGCa and NGCv in the rodent) share some similarities, they exhibit differences in morphology, anatomical links, physiological function and pharmacological characteristics. In this paper, we use the

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terms NGC and the NMC to represent studies in all animals, with the NGC indicating dorsal, and NMC, ventral regions of the medial medulla.

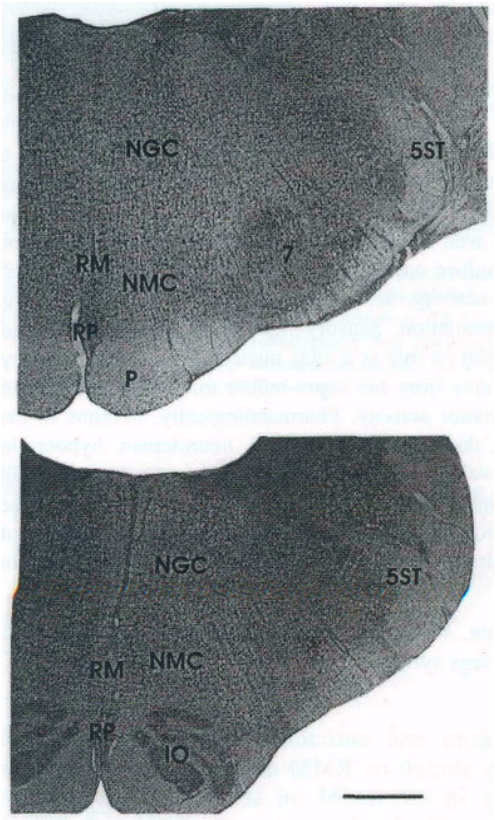

Fig. (1). Histology of the rostral medial medulla in the cat. The term nucleus gigantocellularis alpha is used in the rodent, whereas nucleus magnocellularis (NMC) is preferred in reference to the cat, when designating the ventral part of the rostromedial medulla. IO: inferior olive, NGC: nucleus gigantocellularis, P: pyramidal tract, RM: raphe magnus, RP: raphe pallidus, 5ST: spinal trigeminal tract, 7: facial nucleus. Calibration: 1 mm.

1.2. Phenotypes of NGC/NMC Neuron

The NGC/NMC is a heterogeneous area which contains many neuronal phenotypes. Acetylcholine, GABA, glutamate, and enkephalin are found in NGC neurons [57, 177, 252]. Enkephalin [122, 311, 396], substance-P [71, 311], somatostatin [315], cholecystokinin [237, 439], thyrotropin-releasing hormone [202, 409], neurotensin [18], glutamate [252], GABA [177], glycine [123, 385], acetylcholine [177, 208] and serotonin [202, 261, 262] are used as neurotransmitters by NMC neurons. Nicotinamide adenine dinucleotide phosphate-diaphorase positive neurons, which use nitric oxide as their neurotransmitter, are also found in both NGC and NMC [252].

1.3. Anatomical Link Between NGC/NMC and the Other Areas of the CNS

Neural circuitry can be approached using electrophysiological, pharmacological, and anatomical techniques. Antero- and retrograde axonal transport tracers have shown that the NGC/NMC receives inputs from, and sends efferents to widespread areas of the CNS. These diffuse interconnections between NGC/NMC, and the other areas of the CNS have suggested to some authors that the NGC/NMC plays a role in "level setting" of the excitability of the spinal cord (179).

7.3.7. *Forebrain*

Anatomical studies have demonstrated that neurons in the NGC and NMC project to the cortex [339, 496]. Conversely, projections from the cortex to the NGC and NMC have also been found using anatomical and electrophysiological techniques [12, 165, 172, 220, 240, 340, 392, 399]. Projections from the NGC/NMC to the thalamic nuclei have been identified. The midline and intralaminar thalamic nuclei are related to cognitive control and sleep [95, 136, 198, 227, 329]. They receive strong projections from the NMC and moderate projections from the NGC in the rat [236, 341, 496] and the cat [338, 345]. The motor-related nuclei of the thalamus, the ventrolateral and mediodorsal nuclei, also receive moderate projections from the NGC [298] and a few projections from the NMC [341].

The preoptic nucleus, an area related to sleep induction, has axonal projections to the NMC [436]. In the hypothalamus, the anterior, lateral/posterior, and paraventricular area have strong projections to the NMC and light to moderate projections to the NGC [178, 493]. Neurons in the NGC and NMC also project to the hypothalamus [298, 405, 491]. Reciprocal innervation between Forel's field and the NGC/NMC has also been identified by electrophysiological [192, 193] and anatomical [491, 517] studies.

7.3.2. *Brainstem*

Anatomical studies have shown a very strong reciprocal innervation of the midbrain and the NGC/NMC. Neurons in the mesencephalic reticular formation, the median raphe, and the superior colliculus project to the NGC/NMC [182, 252, 279, 298], with strong innervations of the NMC and ventral NGC [516]. Reciprocal innervation between the NGC/NMC and other areas of the midbrain, such as dorsal raphe, dorsolateral and Pedunculopontine tegmental nuclei has also been demonstrated using anterograde and retrograde transport tracing techniques [205, 252, 421, 491, 492].

The midbrain periaqueductal gray (PAG) and the NMC are anatomically and physiologically linked and function together in the modulation of algesic responses (see below). Neurons in the PAG that project to the NMC are located mainly in the rostral dorsolateral and caudal ventrolateral portions of the nucleus [52, 182, 252, 279, 351, 439, 482, 518]. Using anterograde transport tracing (PHA-L) technique, Farkas *et al.* [115] found that PAG neurons predominantly innervate the NMC with a few projections to the NGC. Conversely, NGC/NMC neurons have been shown to project to the PAG [74, 206].

In the pons, neurons in the pontine inhibitory area [247], which is involved in the regulation of REM sleep atonia, and neurons of the locus coeruleus complex project to the

NGC/NMC [252, 279]. Reciprocally, NGC/NMC neurons send their axonal projections to the locus coeruleus and pontine inhibitory area [206, 298]. In the medulla, the NGC/NMC receives projections from the vestibular nuclei, which are involved in the control of posture, and the rostral ventrolateral medulla [252], which is involved in the regulation of the cardiovascular and respiratory system. Conversely, neurons in the NMC project to the contralateral side of the NMC, and bilaterally to the rostral ventrolateral medulla [41,516] and vestibular complex [141].

1.3.3. Cerebellum

The cerebellum is not a major target of NGC/NMC projections. However, reticulo-cerebellar projection neurons were found in the NGC/NMC of the North American opossum [293] and the cat [102, 414]. Electrophysiological and anatomical studies showed that neurons in the deep cerebellar nuclei, lateral, fastigial, and interpositus, project to the NGC/NMC [35, 185].

1.3.4. Cranial Sensory and Motor Nuclei

The oral motor nuclei, including trigeminal, facial, and hypoglossal nuclei, are functionally related to facial expression, chewing, swallowing, licking and respiration. Intracellular recording in the anesthetized guinea pig demonstrated that stimulation in the NGC/NMC produces excitatory and inhibitory post-synaptic potential (EPSP and 1PSP) in trigeminal motoneurons [144], indicating that neurons in the NGC/NMC project to the trigeminal motor nucleus. Anatomical studies confirmed the projections from the NGC and NMC to the oral motor nuclei [43, 180, 285, 319, 455, 474, 517], although the number of projecting neurons is very small [122]. Glycinergic [386], GABAergic [269] and histological unidentified neurons in the NMC have been found to project to the oral motor nuclei. Neurons in the NGC also project to the other cranial motor nuclei, including oculomotor, trochlear [353, 517], abducens [444], and ambiguus [474]. In the cranial sensory system, NGC/NMC neurons have also been found to project to the trigeminal sensory nucleus [353].

1.3.5. Spinal Cord

It is well-documented that the NGC/NMC and the spinal cord are reciprocally innervated. However, differences in input afferents from, and output efferents to, the spinal cord between the NGC and the NMC have been found. First, NGC/NMC reticulospinal projections mainly originate from the NMC [241]. Second, reticulospinal neurons from the rostral and caudal NMC tend to innervate the dorsal and ventral horn, respectively, whereas descending projections from the NGC are mainly found in the ventral horn, intermediolateral cell column and the sacral paraysmpathetic nucleus [294]. However, descending fibers from the NGC and NMC can be seen in all laminae of the spinal cord [4, 9, 26, 173, 181, 349, 379, 515]. Finally, Hayes and Rustioni [163] and Kausz [218] demonstrated that the NGC projects to the cervical and thoracic, whereas neurons in the NMC project to all segments of the spinal cord, although neurons in the NGC that project to the lumbosacral cord were also reported [368, 426, 457]. Many neurotransmitters employed in the NGC/NMC reticulospinal projection have been identified. Some of reticulospinal neurons from the NGC contain enkephalin and GABA [57, 390]. All phenotypes of transmitter employed by NMC neurons (see Section 1.2) have been reported in projections to the spinal cord [41, 57, 104, 127, 183, 184, 202, 207, 242, 287, 289, 311, 316, 388, 396,409,438,450].

Ascending projections from the spinal cord were also found to innervate the NGC/NMC. Using a lesion technique, Rossi and Brodal [400] and Hazlett *el al.* [164] found that degenerating fibers are present in the NGC/NMC after spinal cord lesion. A retrograde transport tracing study confirmed that NGC/NMC received spinal projections [147]. Axons of ascending spinothalamic and spinohypothalamic neurons have been shown to bifurcate and innervate the NGC/NMC [234, 308]. Neurophysiological study, using unit recording and antidromic stimulation techniques, demonstrated that neurons in the spinal lumbar cord project to the NMC in the cat [58].

2. ELECTROPHYSIOLOGICAL STUDIES OF NGC/NMC IN THE MODULATION OF SENSORY-MOTOR ACTIVITY

Using electrical stimulation and extra- and intra-cellular recording techniques, a relationship between NGC/NMC neuronal activity and sensory/motor activity has been established. Sensory stimuli alter NGC and NMC spontaneous and stimulus-induced firing discharge. Activation of NGC and NMC changes somatomotor and vasomotor activities.

Evidence of the various physiological functions of NGC/NMC described below is derived from studies performed in the behaving, anesthetized, or decerebrate animals. Distinct results may be generated using different types of animal preparations due to interactions of forebrain and brainstem regions of the CNS, and the effect of anesthetics on neuronal activity. In the decerebrate preparation, the forebrain is removed under gas anesthesia and then, gas anesthesia is discontinued because the animal can not perceive pain. Therefore, the decerebrate preparation has been widely used in the study of brainstem modulation of spinal cord uncontaminated by anesthetics or forebrain influences.

2.1. Sensory System

2.1.1. Neuronal Response to Sensory Stimuli

The NGC/NMC receives sensory information from somatic and visceral organs and modulates sensory activity. In 1955, Scheibel *et al.* [414] demonstrated that NGC/NMC neurons respond to sensory stimuli (acoustic click, touch on the nose) in decerebrate and anesthetized cats. In the 1960s and early 1970s, many laboratories studied the responses of NGC/NMC neurons to somatic sensory stimulation. They found that a very high percentage of NGC/NMC neurons responded to somatic noxious (pinching) and innocuous cutaneous stimuli, joint movement, and muscle contraction, as well as visceral noxious stimulus induced by intra-arterial

injection of bradykinin in the anesthetized decerebrate, as well as in the awake animal [54, 55, 142, 378, 420, 506]. Similar findings have also been reported in later studies [37, 38, 113, 268, 333, 357]. The receptive field of some NGC/NMC neurons to cutaneous stimuli is very extensive, covering almost all of the body area [98, 356, 403, 430, 509]. In addition to cutaneous stimuli, neurons in the NGC/NMC are also reported to respond to auditory, visual, and vestibular stimuli [432, 509].

The NGC/NMC also plays a role as the relay nucleus, the spino-reticulo-thalamic pathway, of the sensory system. Bowsher *et al.* [46] reported that NMC bulbo-thalamic projection neurons respond to acoustic, light, non-noxious and noxious cutaneous stimuli. [194].

2.1.2. *Modulation of Sensory Activity*

Neurons in the NGC/NMC not only respond to sensory stimulation, but also modulate behavioral responses to sensory stimuli. Electrical stimulation in the NGC and NMC has been shown to produce inhibitory [120, 412], facilitatory, and biphasic effects [521, 522], on reflex activity induced by noxious and innocuous somatic and visceral stimuli. These results indicate that neurons in the NGC/NMC participate in the regulation of non-noxious and noxious sensation, and that the inhibitory and facilitatory neurons are intermingled in the NGC/NMC. Indeed, unit recording has revealed that noxious related On and Off cells are intermixed in the NGC and NMC [119, 485]. The differential effect on nociceptive responses induced by electrical stimulation of the NGC/NMC may result from activation of either On or Off cells, or both.

At the spinal level, sensory and spinal ascending projection neuronal activity has been shown to be modulated by NGC/NMC stimulation. In 1959, Tolle *et al.* [473] demonstrated that electrical stimulation in the NMC inhibits spinal cord potentials induced by splanchnic nerve stimulation. Stimulation in the NMC also inhibits transmission from primary and cutaneous afferents to motoneurons [197] and from flexor reflex afferent to ascending spinal pathways [106], which are involved in spino-bulbo-spinal reflexes. Extracellular recording demonstrated that electrical stimulation in the NMC and the ventral NGC elicits inhibitory, facilitatory and biphasic effects on the spinal dorsal horn [137, 268, 520, 522] and viscerosomatic [463] neuron activity. Excitatory effect on spinal neuronal activity in laminae VII and VIII, which respond to pinching/squeezing hindlimb muscles, joints, and subcutaneous, induced by stimulation in the NMC were also reported [58]. Spinothalamic tract neurons, which respond to noxious and non-noxious sensory stimuli from hair movement and mechanical stimulation of the skin, are also known to be inhibited and excited by stimulation of the NGC and NMC [94, 131, 148, 149, 303].

Physiological links between NGC/NMC and PAG involvement in nociception have been well-studied. It has been suggested that antinociception induced by electrical and chemical stimulation in the PAG is mediated through the NGC/NMC. Activation of the PAG produces analgesia, while simultaneously changing firing rates in neurons located in the NGC and NMC [321, 325]. On the other hand, inactivation of the NMC induced by lidocaine injection significantly increases the stimulation current required in the PAG for induction of analgesia [407] and decreases the analgesic response induced by morphine injection into the PAG [480]. Electrolytic lesion of the NMC has also been reported to abolish analgesia induced by the injection of neurotensin into the PAG [30].

2.2. **Motor Activity**

Stimulation of NGC/NMC produces either facilitatory or inhibitory effects on motor activity. The effect of NGC/NMC activation on motor activity depends on the site of stimulation, stimulation parameters, animal preparation and sleep-waking states. In general, stimulation in the medial portion of the NGC/NMC produces inhibition, whereas stimulation of the lateral portion produces either inhibition, or inhibition followed by facilitation of motor activity, in decerebrate and in anesthetized animals [233, 278, 283, 284]. The posture of the animal is a factor in determining the motor responses to NGC/NMC stimulation. Inhibition of somatic and visceral reflexes [8], global muscle atonia [145, 151, 243], and muscle relaxation [284] were observed when NGC/NMC stimulation was applied in the decerebrate animal, which was not supported by a moving treadmill. However, stepping-like activity can be generated by NGC/NMC stimulation, when decerebrate or anesthetized animals are placed on a moving treadmill [346, 397]. The stimulation parameters have a major role in determining whether stimulation has an inhibitory or facilitatory effect on motor activity. Low intensity stimulation tends to induce inhibition, whereas high intensity stimulation produces either inhibition followed by facilitation, or facilitation [151, 243], Finally, motor responses to NGC/NMC stimulation depend on sleep-waking states in the behaving animal. Stimulation applied during waking produced head movement, elbow flexion and extension, increases in tonic neck muscle activity [96, 97] and escape behavior [56]. On the other hand, stimulation, which increased muscle tone during waking, induced suppression of muscle tone during sleep [418].

NGC/NMC is required for both mesencephalic locomotion region stimulation induced locomotion, and pontine inhibitory area stimulation induced muscle atonia in decerebrate and in anesthetized animals. Inactivation of NGC/NMC by cooling, chemical injection, and lesion either blocked stepping induced by mesencephalic locomotion region stimulation, or increased the threshold for mesencephalic locomotion region stimulation to induce locomotion [290, 347, 423]. Our study showed that microinjection of glutamate antagonists into the NMC reversed muscle tone suppression induced by pontine carbachol injection [244], Indeed, Iwakiri *et al.* [195] demonstrated that stimulation in the mesencephalic locomotion region and pontine inhibitory area activates different populations of NGC/NMC reticulospinal neurons, and produces locomotion and muscle tone suppression, respectively. However, lesions in the NGC/NMC in the behaving animal produce a temporary motor deficit during waking and permanent rapid eye movement (REM) sleep without atonia [177, 417], indicating that the NGC/NMC plays an important role in the regulation of muscle activity during sleep.

Unit recording studies have confirmed that neuronal activity in the NGC/NMC is related to motor activity. The activity of subpopulations of NGC/NMC neurons correlates with axial, limb, eye, and facial movement during waking [432, 433], as well as REM sleep phasic and tonic muscle activity [431, 489] in the behaving animal. In decerebrate animals, NGC/NMC neuronal activity has been found to correlate with spontaneous and mesencephalic locomotion region induced locomotion walking on treadmills [365].

2.3. **Cardiovascular and Respiratory Activities**

As early as 1939, Pitts *el al.* [376] reported that electrical stimulation in the NGC and NMC produces opposite effects on respiratory activity, with the NMC and NGC related to inspiration and expiration, respectively. Their findings were confirmed in other laboratories. Electrical stimulation in the NMC increases respiratory [343] and phrenic nerve activity [510], whereas stimulation in the NGC produces a decrease in respiratory rate, tidal volume and amplitude of phrenic nerve activity in anesthetized cats [451]. Our recent study found that stimulation in the NGC either decreases the amplitude of diaphragm activity, or terminates inspiration in the decerebrate animal [254]. On the other hand, stimulation of NMC caused an increase in the amplitude of diaphragm EMG and prolonged diaphragm activity when the stimulation was applied during inspiration, whereas diaphragm activity (inspiration) was activated when stimulation was applied during expiration [254]. Unit recording has shown that the firing pattern of NMC neurons is correlated with inspiratory activity in the anesthetized cat [146]. Thus, lesions in the NMC cause a decrease in tidal volume [447] and block hyperpneic and tachypneic responses to hypercapnea [318]. Lesions in the NGC cause an increase in tidal volume and respiratory frequency induced by stimulation of the hypothalamic locomotor region [393].

Stimulation in the NGC/NMC also induces a change in cardiovascular activity. Unlike respiratory activity, which showed an opposite effect after NGC and NMC stimulation, activation of both the NGC and the NMC produced a reduction of mean arterial pressure and heart rate in the decerebrate and anesthetized cat [60, 61, 238, 394, 451]. The same stimulation caused an 80-92% inhibition of the cardiac sympathetic, and a 45-58% inhibition of cardiac vagal nerve activity in the anesthetized cat [510].

2.4. Convergence of Somatic and Visceral Inputs and Divergent of Somatic and Visceral Outputs of the NGC/NMC

NGC/NMC neurons were found to respond to innocuous and noxious somatic stimuli, as well as to increase in blood pressure induced by systemic administration of norepinephrine and occlusion of the descending aorta in the α-chloralose anesthetized cat [509]. Unit recording revealed that an increase in mean arterial blood pressure elicited both a decrease and an increase in spontaneous NGC/NMC somatic noxious On- and Off-cell activity, respectively [470]. Stimulation of vagal afferents inhibited 60% of Off-cells, whereas the same stimulation excited all On-cells, indicating that activation of baroreceptors modulates somatic noxious On- and Off-cell activity [470]. On the other hand, activation of NGC/NMC inhibited the activity of both somatic and visceral spinal ascending projection neurons [62].

Stimulation of NGC/NMC also induced change in somatic and autonomic motor activities. In 1952, Bach [22] reported changes in the patellar tendon reflex with simultaneous changes in respiratory and vasomotor activity, when the NGC/NMC is activated in anesthetized and decerebrate cats. Our study also showed that microinjection of glutamate into the NMC elicited a suppression of muscle tone and simultaneously decreased blood pressure [246] (see Pharmacology section)

2.5. Sleep

Sleep is homeostatically regulated and includes changes in autonomic and somatic activities and hormone secretion. Neurons in many areas of the CNS change their firing pattern across the sleep cycle. In 1949, Moruzzi and Magoun [329] first demonstrated that activity of the NGC/NMC is related to electroencephalographic (EEG) desynchronization. They used high frequencies, up to 300 Hz, to stimulate the NGC/NMC and found that this produced a desynchronized cortical EEG in the chloralose anesthetized cat. They concluded that NGC/NMC activity is related to waking. However, using low frequency (14 Hz) stimulation of the NGC/NMC, Favale *et al.* [116] found that EEG synchronization was seen after the second pulse of stimulation. They also found that NGC/NMC stimulation had no effect on cortical activity during fully activated EEG desynchronization, but that a synchronized EEG can be induced when stimulation is administered in the animal during drowsy state with light EEG desynchronization. Their findings suggest that the effect of NGC/NMC activity is state-dependent. State-dependent firing was reported by our laboratory as well as other laboratories. The sleep-related neurons recorded in the NGC/NMC can be divided into 2 categories. Movement-related neurons have a high firing rate during waking with movement and in REM sleep. Sleep-related neurons in which firing rate was minimal in active waking and increased during quiet waking and slow wave sleep (SWS) with maximal firing in REM sleep [214, 264, 430, 431, 489].

The REM sleep active cells in the NGC/NMC may be involved in the suppression of muscle tone [214], because stimulation in this region during REM sleep induced hyperpolarization of motoneurons [63]. Eesions in this area produced an increase in tonic and phasic muscle activity during REM sleep [177, 417]. The motoneuron response to NGC/NMC stimulation is state-dependent. Intracellular recording has demonstrated that electrical stimulation in the NGC/NMC produced hyperpolarization of the spinal and trigeminal motoneuron during natural and carbachol-induced REM sleep, with no effect on motoneuron excitability during waking and SWS [64, 364]. Our study, recording from neck muscles in the behaving cat, showed that electrical stimulation in the NGC/NMC also produced a state-dependent change in muscle tone [418] (also see Section 2.4). We found that electrical stimulation of the NGC/NMC induces muscle atonia during SWS in the behaving cat (Fig. 2). These results indicate that the NGC/NMC is required for inducing muscle

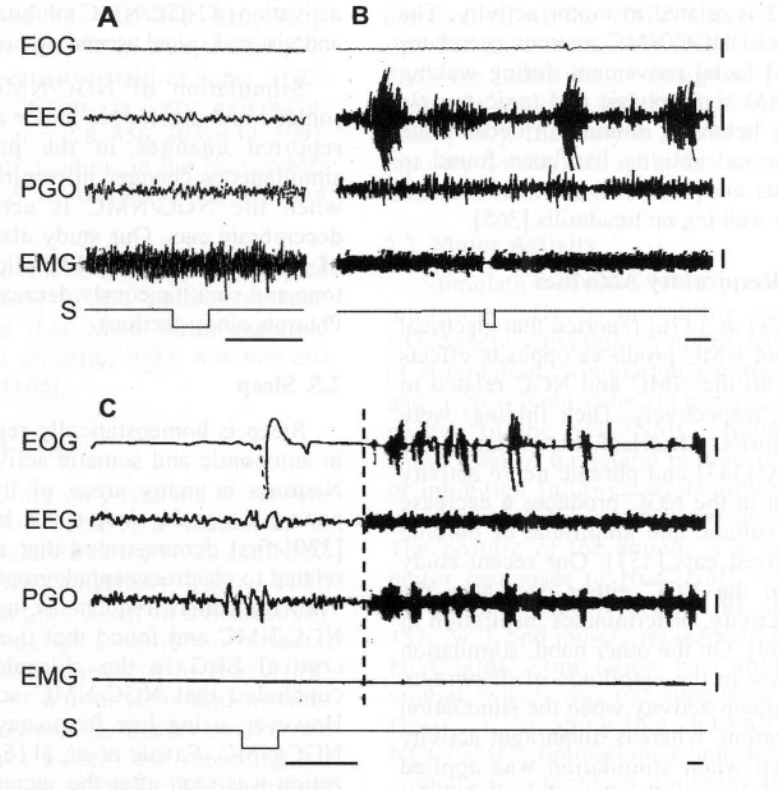

Fig. (2). Effect of sleep states on muscle responses to medial medullary stimulation. Electrical stimulation (150 Hz, 50 μA and 0.2 ms rectangular pulses; train duration, A and C: 500 ms, B: 300 ms) administered into the nucleus gigantocellularis produces state-dependent muscle responses in the behaving cat. Stimulation applied into the NGC produces no change in muscle tone during waking (A), suppression in muscle tone (atonia) during slow wave sleep (B). Muscles are atonix during normal REM sleep and stimulation produces no further change in REM sleep (C). EEG: electroencephalogram; EMG: electromyogram; EOG: electro-oculogram; PGO: pontogeniculoocular spike, S: electrical stimulation. Calibration, 100 μV and 1 sec.

atonia. Activation of the NGC/NMC exerts an inhibitory effect on motoneurons during SWS, which resembles that normally seen during REM sleep.

The response of the NGC/NMC neurons to sensory input is also state-dependent. Okuma and Fujimori [355] demonstrated that NGC/NMC neuronal responses to cutaneous stimulation are decreased during SWS and further suppressed during REM sleep, when compared with waking. Leung and Mason [264] found that the firing of the NGC/NMC cells responsive to noxious stimuli did not differ between waking and SWS. In contrast, the spontaneous activity of both noxious On- and Off-cells was altered across the sleep cycle. Most of the noxious On-, Neutral-, and unclassified neurons were wake-active, having a higher discharge rate during waking than that in SWS. On the other hand, the majority of noxious Off-cells were SWS active, showing a higher firing during SWS than during waking.

3. PHARMACOLOGICAL CHARACTERIZATION OF THE NGC/NMC

The effect of agonists and antagonists on behavioral responses and neuronal activity can be approached by using microinjection and iontophoretic injection techniques. Several putative neurotransmitters have been shown to modulate sensory (Fig. 3) and motor (Fig. 4) responses when injected into the NGC/NMC. Unlike electrophysiological studies, which were performed in both NGC and NMC, most pharmacological studies have been performed in the NMC. Therefore, this section will primarily discuss pharmacological studies in the NMC.

3.1.Opioids

3.7.7. *Classification of Opioid Agonists*

Drugs, natural and synthetic, with morphine-like activity are referred to as opioids. Three endogenous opioid families, the enkephalins, the endorphins, and the dynorphins, have been chemically isolated and purified. Each family is derived from a distinct precursor, proopiomelanocortin (endorphin), proenkephalin (Met-enkephalin), or prodynorphin (Leu-enkaphalin and dynorphin). In general, morphine and Met- and Leu-enkaphalin activate the μ-opioid receptor, whereas endorphin and dynorphin activate δ- and K-opioid receptors. respectively.

5.7.2. *Opioid Receptors*

The existence of multiple opioid receptors has been well-documented. In 1976, Martin and his colleagues [296]

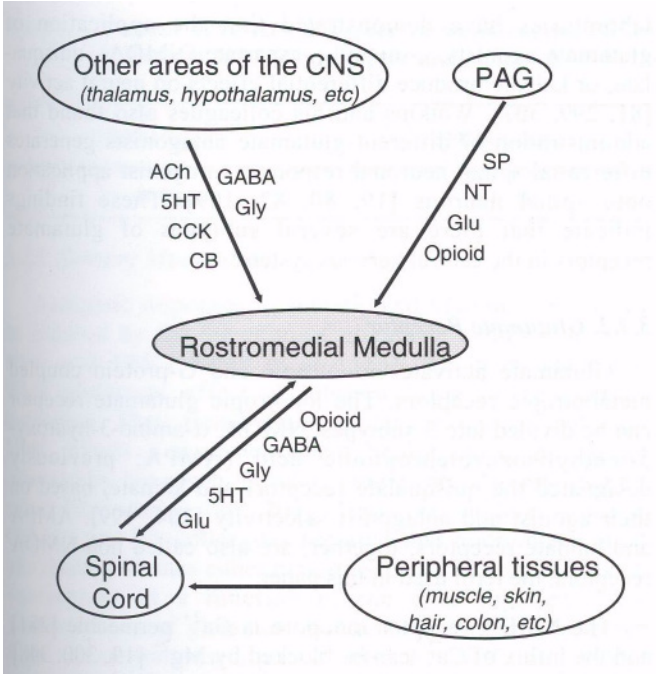

Fig. (3). Schematic of rostromedial medulla pathways involved in the modulation of sensory systems. Sensory inputs from either the spinoreticular neurons or spinothalamic neurons bifurcate and innervate the NGC/NMC. The effect of NGC/NMC on sensory modulation can be influenced by the periaqueductal gray (PAG) and the other areas of the CNS. Putative neurotransmitters used for the projecting neurons are listed along arrows. Ach: acetylcholine; CB: cannabinoid; CCK: cholecystokinin; Glu: glutamate; Gly: glycine; NT: neurotensin; SP: substance P; 5HT: serotonin.

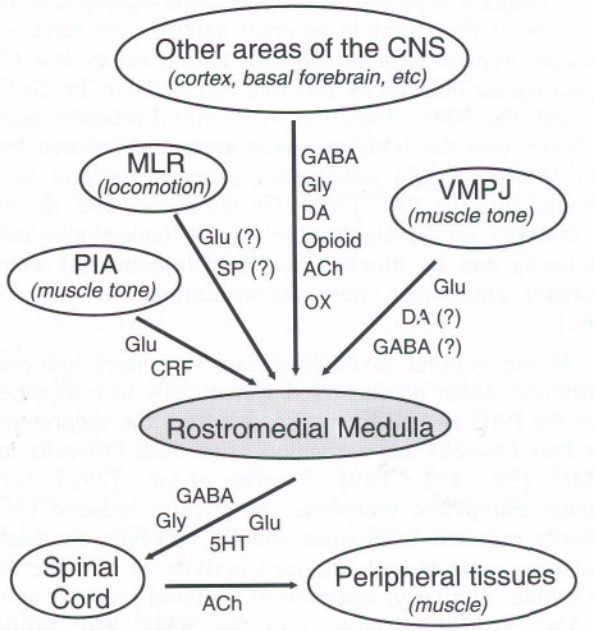

Fig. (4). Schematic of rostromedial medulla and its pathways involved in the modulation of motor system. The rostromedial medulla modulates motor activity via inhibitory GABAergic and glycinergic, as well as excitatory glutamatergic and serotonergic reticulospinal neurons. Activity of the NGC/NMC is affectecd by the inputs from the higher motor regulatory centers, such as pontine inhibitory area (PIA), mesencephalic locomotion region (MLR) and ventral mesopontine junction (VMPJ). CRF: corticotropin-releasing factor; DA: dopamine; OX: orexin (hypocretin).

identified 3 opioid receptors, μ, κ, and /o, based on their physiological responses to morphine- and nalorphine-like drug administration in chronic spinal dogs. It was later found that the o receptor does not belong to the opiate family [381], because opiate-related compounds, morphine and naloxone, exhibited very low affinities for the receptor [258]. In 1977, Lord *et al.* [275] studied the binding affinity of endogenous opioid peptides to mouse vas deferens and guinea pig ileum. They proposed that an additional receptor, the 5-opioid receptor, existed. Each opioid receptor has a unique distribution in the central nervous system, with μ and § opioid receptors predominantly found in the cortex and forebrain. All 3 opioid receptors are found in the NGC and NMC [88, 92, 212, 286, 289, 327, 497], with μ-opioid receptor located postsynaptically and 5-opioid receptor located presynaptically [213].

3.1.3. Sensory Modulation

Opioids are well-known to regulate the pain response. The neural circuitry of opiate-related nociception involves the PAG and the NGC/NMC [27]. Electrical stimulation, as well as opioid agonists and GABA antagonists injected into the PAG induced analgesia [112, 270, 321, 402]. Analgesia induced by activation of PAG had been hypothesized to be mediated through the NGC/NMC, because opiate antagonists [402] injected into the NGC/NMC attenuated PAG induced antinociception.

Akaike *et al.* [7] and Dickenson *et al.* [91] used a microinjection technique to examine the functional relations between the NGC/NMC-opioid system and nociception. They found that the injection of morphine into the nucleus raphe magnus, the NGC, and the NMC induced an analgesic response, which can be reversed by systemic injection of the opioid antagonist, naloxone. Conversely, injection of naloxone into the NMC blocked the systemic morphine injection-induced antinociceptive response [91]. Other studies showed that injection of enkephalin and morphine into the NMC and NGC produced a dose-dependent increase in the latency of nociceptive reflexes [130, 200, 475]. These results indicate that the μ-opioid receptor in the NGC/NMC is involved in the analgesic response.

Algesic responses were also induced by activation of 5-opioid receptor in the NGC/NMC. Both the specific δ_1-opioid receptor agonist, [$_D$-Pen^2,$_D$-Pen^5]enkephalin and the 52-opioid receptor agonist, [$_D$-Ala^2, Glu^4]deltorphin injected into the NMC induced an increase in latency of the tail-flick in the rat [158, 189, 398, 469]. The effect of δ_1- and δ_2-opioid receptor agonists on nociceptive responses can be blocked by local NGC/NMC injection of δ_1-, 7-benzylidenenaltrexone and [$_D$-Ala^2-Leu^5-Cys^6]enkephalin, and δ_2-, naltriben, opioid receptor antagonists, respectively [398,469].

In contrast to μ- and δ-opioid receptor agonists, systemic infusion of the K-opioid receptor agonist, ethylketazocine, induced hyperalgesia in the skin twitch reflex test [507]. Hyperalgesia induced by K-opioid receptor may be mediated through the NMC. Injection of κ opioid receptor agonist, U69593, into the NMC reversed analgesia induced by [D-Ala^2,MePhe^4,Gly(ol)^5]enkephalin, μ,-opioid receptor agonist, injected into the PAG [361]. On the other hand, the effect of U69593 on [$_D$-Ala^2,MePhe^4,Gly(ol)^5]enkephalin-induced analgesia can be blocked by prior injection of K-opioid receptor antagonist, norbinaltorphimine, into the NMC [361].

At the cellular level, analgesic responses induced by morphine, either administered systemically or microinjected into the PAG and NMC, may result from the suppression of noxious On-cells and activation of noxious Off-cells in the NMC [28, 112, 169]. Martin *et al.* [292] further demonstrated that morphine specifically reduced On-cell activity response to noxious stimuli, however, spontaneous and innocuous stimuli induced activity is not altered by morphine. Similarly, injection of 8 opioid receptor agonist, [$_D$-Ala^2, Glu^4]deltorphin, into the NMC also produces inhibitory and facilitatory effect on On- and Off-cell activity, respectively [158].

3.1.4. Motor Modulation

The functional effect of the opioid system in the NGC/NMC on motor activity is not clear. Morgan and Whitney [326] reported that injection of morphine into the NMC produces a decrease in open field activity. Our study (unpublished data) found that microinjection (0.3 μl) of dynorphin A_{1-13}, a K-opioid receptor agonist, at a dose of 3 picomole into the NMC produced muscle tone suppression in the decerebrate cat. The same injection also blocked spontaneous and sensory-induced myoclonus induced by ventral mesopontine junction lesion in the decerebrate cat. In contrast, injection of [$_D$-Ala^2,MePhe^4,Gly(ol)^5]enkephalin and ß-endorphin, both μ-opioid receptor agonists, as well as [D-Pen^2,$_D$-Pen^5]enkephalin, a 5-opioid receptor agonist, into the NMC did not change muscle activity. Those results indicate that activation of NMC K-, but not JJ,- and δ-opioid receptor, may be involved in the regulation of motor activity.

3.2. **Glutamate**

Glutamate is the major excitatory neurotransmitter in the CNS. Anatomical studies have demonstrated that glutamate immunoreactive perikarya, fibers, and terminals can be seen throughout the brain and spinal cord.

3.2.1. *Classification of Glutamate Agonists*

Glutamate was found to exert an excitatory effect on neuronal activity as early as the 1950's [76, 162]. It was hypothesized that glutamate depolarizes the neuronal membrane via an increase in Na^+ conductance [78, 187, 277]. The glutamate effect on neuronal activity can be antagonized by many varieties of dipeptide, such as γ-D-glutamyglycine (DGG) and $_L$-glutamic acid diethyl ester (GDEE). Both of these are non-selective glutamate antagonists [204]. Using pharmacological techniques, many laboratories have demonstrated that the application of glutamate agonists, $_N$-methyl-$_D$-aspartate (NMDA), quisqua-late, or kainate produce differential effects on neural activity [81, 299, 307]. Watkins and his colleagues also found that administration of different glutamate antagonists generates differential spinal neuronal responses to agonist application onto spinal neurons [19, 80, 82, 109]. These findings indicate that there are several subtypes of glutamate receptors in the central nervous system.

3.2.2. *Glutamate Receptor*

Glutamate activates ionotropic and G-protein coupled metabotropic receptors. The ionotropic giutamate receptor can be divided into 3 subtypes, NMDA, α-amino-3-hydroxy-5-methylisoxazolepropionic acid (AMPA; previously designated the quisqualate receptor) and kainate, based on their agonist and antagonist selectivity [204, 499]. AMPA and kainate receptors, together, are also called non-NMDA receptors, the term used in this paper.

The NMDA receptor ionopore is Ca^{2+} permeable [281] and the influx of Ca^{2+} can be blocked by Mg^{2+} [19, 300, 348] and Zn^{2+}[240, 323]. It was originally demonstrated that activity of the NMDA receptor can be potentiated by glycine [203]. Later studies found that glycine binds to a strychnine-insensitive site [203] and is required for activation of the NMDA receptor [230]. NMDA but not non-NMDA receptor activity can be blocked by D(-)-2-amino-5-phosphonovalerate (APV) and longer chain phosphonates [82, 110]. However, there is no antagonist that specifically blocks non-NMDA receptors. Though quinoxaline-diones, 6-cyano-7-nitroquino-xaline-2,3-dione (CNQX) and 6,7-dinitroquinoxaline-2,3-dione(DNQX), are relatively selective blockers of the non-NMDA receptor [186], they also antagonize the NMDA receptor by competing with glycine for the modulatory site of the receptor complex [36, 223, 263, 387].

The metabotropic glutamate receptor (mGluR) contains 6 subunits, mGluRl — mGluR6. The mGluR subunits can be divided into 3 groups, mGluR1/5, mGluR2/3, and mGluR4/6. The mGluRl/5 subunit is coupled to stimulate phospholipase C activity, which triggers inositol phosphate formation, Ca^{2+} release, and then activates a Ca^{2+}-activated Cl^- channel [188, 375]. The mGluR2/mGluR3 and mGluR4/ mGluR6 groups are coupled with the inhibitory cAMP cascade and involved in inhibitory neurotransmission [334, 458, 459]. The difference between these two groups is that trans-l-aminocyclopentane-l,3-dicarboxylic acid and L-2-amino-4-phosphobutyric acid, are potent activators of mGluR2/mGluR3 and mGluR4/mGluR6 subunits, respectively [188, 458].

Glutamate immunoreactive neurons are found in the NGC and NMC [252]. Neurons in the NGC and NMC also express NMDA and non-NMDA receptors [369, 370, 411, 498]. Using a double labelling technique, we found that NMC contains neurons single labeled for NMDA, AMPA, and kainate receptors, as well as neurons double-labeled for NMDAαMPA and NMDA/kainate receptors [248, 249], A very high percentage of NMC neurons contained more than one subtype of glutamate receptor (Table 1).

Table 1. Percent of NMDA Receptor Immunoreactive Positive Neuron Co-localized with AMPA (GluRl, GluR2/3, GIuR4) and Kainate (GluR5/6/7) Receptor Immunoreactivity in the NMC

NMDA/GluRl	NMDA/GluR2/3	NMDA/GluR4	NMDA/GluU5/6/7
49.3%	63.0%	57.3%	56.4%

3.2.3. Sensory Modulation

Analgesic responses to somatic and visceral stimuli can be induced by the injection of glutamate agonists into the NGC and NMC. Satoh *et al.* [413] first investigated the NMC-glutamate effect on algesia using microinjection technique. They found that $_{L}$-glutamate injected into the NMC elicits a dose-dependent analgesia in the rat as assessed by tail pinch. Similar findings are also reported by other laboratories [20, 201]. However, in later studies, Gebhart and his colleagues reported that microinjection of glutamate generates either inhibitory or facilitatory effects on nociception as a function of the dose injected. Low concentrations of glutamate induced hyperalgesia, whereas high concentrations injected into the NGC and NMC produced analgesia [520, 522].

Specific glutamate receptor agonists and antagonists were used to determine the type of glutamate receptors involved in the modulation of NGC/NMC effects on algesia. Analgesia induced by glutamate injected into the NGC/NMC can be blocked by the non-specific glutamate antagonist, DGG, and the specific NMDA antagonist, APV, in awake and anesthetized rats, indicating that the NMDA receptor is involved in NGC/NMC-analgesia [6]. Non-NMDA and mGlu receptors are also involved in NGC/NMC-glutamate-induced analgesia. Kainate, as well as 2',3'-dicarboxycyclopropyl glycine and *trans*-l-aminocyclopentane-l,3-dicarboxylic acid, a mGluRl and a mGluR2 receptor agonist, respectively, injected into the NMC and the ventral portion of the NGC produced a dose-dependent inhibition of tail flick and hot-plate responses [225, 326]. The mGluR receptor agonist effect on the nociceptive response can be blocked by the selective mGluR receptor antagonist, (RS)-α-methyl-4-carboxyphenylglycine, but not naloxone [225]. Injection of the NMDA receptor antagonist, APV and MK-801, and non-NMDA receptor antagonist, CNQX, into the ventral NGC and NMC elicited a reduction of PAG opioid-induced analgesia [446].

Descending adrenergic, GABAergic, and serotonergic mechanisms may be involved in the glutamate effect on algesia. Satoh *et al.* [413] found that NMC-glutamate induced analgesia can be reversed by intrathecal administration of the α-adrenergic antagonist (phenoxybenzamine and phentolamine), but not serotonin (methysergide), opioid (naloxone), and ß-adrenergic (propranolol) antagonists. They hypothesized that the descending noradrenergic system, acting via α-adrenergic receptors, plays an important role in the modulation of pain response. However, whether a descending serotonergic mechanism is involved in the glutamate effect on algesia remains unclear. McGowan and Hammond [304] demonstrated that intrathecal injection of methysergide completely blocked antinociception induced by glutamate injection into the NMC in the tail flick test. Zhuo and Gebhart [519] reported that intrathecal injection of high, but not low, concentrations of methysergide attenuated NGC/NMC electrical stimulation induced analgesia. A GABA mechanism has also been demonstrated to be involved in NMC-glutamate induced analgesia. It has been shown that analgesia induced by glutamate injection into the NMC can be attenuated by intrathecal administration of bicuculline, a GABAA receptor antagonist, and enhanced by diazepam, a $GABA_A$ receptor agonist, indicating that a GABAA mechanism is involved in analgesia induced by glutamate injection [305].

3.2.4. Motor Modulation

Microinjection of glutamate into the NMC produces a change in muscle tone and motor activity. This glutamate effect on the regulation of motor activity is site- and receptor subtype-specific. Glutamate injected into the NMC, but not the NGC, elicited generalized muscle tone suppression in the decerebrate cat [244]. The effect of glutamate on muscle activity can be blocked or attenuated by glutamate antagonists, DGG and GDEE, previously injected into the same NMC site [244]. Using relatively specific NMDA and non-NMDA receptor agonists, we found that NMDA and non-NMDA receptor agonists microinjected into the NMC elicit opposite effects on muscle activity. Activation of the NMDA receptor produced an increase in muscle tone and/or locomotion [151, 247], whereas activation of non-NMDA receptors by kainate and quisqualate injection produced muscle atonia [151, 247]. Kinjo *et al.* [226] also reported increased motor activity after NMDA injection. The effect of NMDA and non-NMDA agonists on muscle activity can be blocked by APV and CNQX/DNQX, respectively [151, 226, 247]. In the behaving rat, application of kainate into the NMC induced immobility [326]. These results support our hypothesis that facilitation and inhibition of motor activity are mediated through NMDA and non-NMDA mechanisms in the NMC, respectively. Activation of non-NMDA receptors in the NMC has been suggested to relate to REM sleep atonia. Indeed, Kodama *et al.* [231] found that glutamate release in the NMC, measured by *in vivo* microdialysis and HPLC analysis, increased during REM sleep in the behaving cat.

Specific NMDA and non-NMDA receptor activation-induced muscle tone facilitation and inhibition has been further investigated through the use of microinjection of glutamate receptor agonists and antagonists into the NMC during muscle abnormalities caused by damage to supra-medullary structures. Glutamate receptor antagonists, APV, DGG, GDEE, and CNQX, microinjected into the NMC alone produced no effect on muscle activity [151, 244, 247], indicating that glutamate is not tonically released. However,

the glutamate antagonist, DGG, injected into the NMC reversed muscle tone suppression induced by stimulation of the pontine inhibitory area with carbachol injection [244]. This result indicated that muscle atonia induced by pontine inhibitory area activation during REM sleep is mediated through aglutamatergicmechanism in theNMC. Furthermore, phasic muscle activity may also be mediated by the NMC-glutamate system. Our studies using the decerebrate cat found that lesion of the ventral mesopontine junction, including the caudal part of the ventral tegmental area and retrorubral nucleus in the midbrain and the rostroventral part of the paralemniscal tegmental area in the pons, produced spontaneous or sensory stimuli-induced muscle twitches [250]. This muscle hyperactivity induced by ventral mesopontine junction lesion can be attenuated or blocked by injection of the NMDA antagonist, APV, and non-NMDA agonist, kainate, quisqualate, and willardine, into the NMC [251]. We have hypothesized that the ventral mesopontine junction triggers phasic muscle activity *via* the NMC during sleep [251]. Our anatomical study, using retrograde transport of WGA-HRP combined with immunohistochemistry, demonstrated that the NMC receives glutamatergic projections from both the pontine inhibitory area and ventral mesopontine junction [252].

In contrast to our finding that glutamate injected into the NMC produces muscle atonia, Noga *et at.* [346] found that that injection of glutamate into the NMC produces locomotion in decerebrate animals walking on a moving treadmill. The discrepancy between these studies could result from the technique used and the volume (of 5 µl by Noga *et al. vs.* 0.5 µl by Lai and Siegel) injected. Our animals sat quietly, while their animals received continuous sensory inputs from the moving treadmill. Sensory input itself may trigger locomotion. Indeed, Aoki and Mori [13] showed that pinna stimulation is able to induce locomotion in the decerebrate cat walking on the moving treadmill. Locomotion induced by injection of high volume (5 µ1/0.1 M) of glutamate into the NMC could result from chemical diffusion to the lateral part of the medullary locomotor strip. The mean latency for locomotion induced by glutamate injection into the NMC is as long as 30 min [346]. In contrast, low volume (0.5 µl/0.1 M) glutamate injection, used in our study, produced muscle tone suppression with a latency of 18 sec [244].

3.2.5. Cardiovascular-pulmonary Modulation

A glutamatergic mechanism in the NGC and NMC has been shown to be involved in the regulation of cardiovascular activity. Microinjection of glutamate into the NGC and NMC produces a decrease in blood pressure, and a decrease or no change in heart rate in the rat [4] and cat [246, 452, 510]. However, both pressor and depressor responses can also be elicited by NMDA microinjected into the NGC and NMC [487], indicating facilitatory and inhibitory neurons are intermingled in the NGC and NMC. These NGC/NMC-glutamate induced cardiovascular changes can be blocked by a prior injection of non-specific glutamate antagonists, DGG and GDEE, as well as the specific NMDA antagonist, APV [246]. Glutamate-induced change in cardiovascular activity may be mediated through the dorsal motor nucleus of the vagus and nucleus tractus solitarius [452], and/or through the NGC/NMC bulbospinal projection [463]. Cardiovascular changes induced by glutamate injection into the NMC have been postulated to be mediated through activation of GABAergic neurons, which project to the thoracic preganglionic neurons [5]. Fifty-four percent of the synapses found in the intermediolateral cell column innervated by NMC are symmetric [5], indicating inhibitory function [366]. In the pulmonary system, glutamate agonists, glutamate and kainic acid, microinjected into the NGC elicit a decrease in respiratory rate and tidal volume [451].

3.3. Inhibitory Amino Acids

GABAergic and glycinergic neurons are anatomically segregated in the CNS, with GABAergic neurons predominantly located in the rostral brain and glycinergic neurons located predominantly in the caudal brain and spinal cord. Recently, pharmacological and anatomical studies found that GABA is potentially as important as glycine in the regulation of physiological functions in the caudal brain and spinal cord.

3.3.1. GABA

Twenty to fifty percent of the CNS synapses are GABAergic [42, 512], making it the most abundant inhibitory synapse. The majority of GABAergic neurons act as interneurons. However, many GABAergic neurons, such as GABAergic reticulospinal neurons, project to distant targets [183].

3.5.1.1. GABA Receptor

GABA receptors can be divided into 3 types, $GABA_A$ $GABA_B$, and GABAc, based upon their affinity for agonists and antagonists. The $GABA_A$ receptor can be activated by muscimol and isoguvacine and inhibited by bicuculline, picrotoxin, and gabazine. The $GABA_B$ receptor is activated by (-)-baclofen and inhibited by phaclofen and saclofen. The GAB AC receptor is activated by muscimol and *cis-4*-aminocrotonic acid and inhibited by imidazole-4-acetic acid and picrotoxin[44]. Benzodiazepines [404, 435], barbiturates [367, 472], steroids, and ethanol [159, 350, 391] bind to $GABA_A$ receptor and potentiate GABAergic transmission. $GABA_A$ and $GABA_B$ receptors are found in NGC/NMC [45, 154, 288, 508] reticulospinal neurons, which project to the dorsal horn [154, 508]. Electrophysiological study has demonstrated that spontaneous firing of reticulospinal neurons in the NGC/NMC is inhibited by iontophoretic application of GABA [363].

3.3.1.2. Pain Modulation

Although one study has shown that GABA injected into the NMC did not change tail flick latency [20], other studies have demonstrated that a GABAergic mechanism is involved in the NMC algesic response. Microinjection of the $GABA_A$ receptor agonists, 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol and muscimol, into the NMC significantly decreased tail flick latency [100]. In contrast, injecting the $GABA_A$ receptor antagonist, bicuculline, into the NMC produced a significant increase in tail flick latency [100], which could be

attenuated by a prior injection of 4,5,6,7-tetrahydroisoxazolo [5,4-c]pyridin-3-ol [167], a $GABA_A$ receptor agonist. This result indicates that activation of the $GABA_A$ receptor in the NMC elicits a hyperalgesic response. GABAA receptor mediated modulation of pain response could result from changes in noxious Off-cell activity. Prolonged firing of noxious Off-cell can be induced by iontophoretic application and microinjection of bicuculline into the NGC and NMC [170].

The effect of $GABA_B$ receptor in the NGC/NMC on algesic response was determined using a microinjection technique. Injection of baclofen, a $GABA_B$ receptor agonist, into the NGC and NMC produced an increase in tail flick latency [266]. Thomas *et al.* [467] reported that the effect of $GABA_B$ receptor activity on algesic response is dose-dependent. A low dose (0.1-1.0 ng) of baclofen injected into the NMC increased tail flick latency, whereas a high dose (30-150 ng) injected into both the NGC and the NMC caused a decrease in tail flick latency. The low dose baclofen effect on tail-flick reflex latency can be blocked by intrathecal treatment of methysergide [156]. They hypothesized that a low dose of baclofen activates pre-synaptic $GABA_B$ receptors and inhibits GABA release onto the nucleus, which in turn disinhibits bulbospinal serotonergic neuron activity and increases serotonin release in the spinal cord [156]. In contrast, a high dose of baclofen not only activates pre-synaptic $GABA_B$ receptors, but also causes post-synaptic $GABA_B$ receptor activation, which hyperpolarizes and inhibits NGC/NMC neuron activity [467].

3.3.1.3 Motor Modulation

As early as the 1960s, several laboratories demonstrated that glycine and GABA can modulate motoneuron activity. Intravenous injection of picrotoxin suppressed pre-synaptic inhibition, whereas injection of strychnine, a glycine antagonist, inhibited post-synaptic inhibition in spinal motoneurons induced by NGC/NMC stimulation of the cat [274], Injection of $GABA_A$ agonists, GABA and muscimol, into one side of the NMC blocked contralateral NMC electrical stimulation-induced locomotion. In contrast, injection of $GABA_A$ antagonists, bicuculline and picrotoxin, into the NMC induced stepping-like activity [226], indicating that a GABAergic mechanism is required in the suppression of motor activity. The effect of $GABA_B$ receptor activity on motor behavior was also studied by Thomas *et al.* [467]. They found that baclofen microinjected into the NGC/NMC produces motor disturbances, such as tilting of the body and circling on the hot plate.

3.3.2. Glycine

Glycine and GABA have closely related mechanisms of action. Unlike GABA, which is widespread in the CNS, glycine is more restricted and predominantly located in the spinal cord and brainstem [14].

3.3.2.1. Glycine Receptor

Two subunits, a and (3, of glycine receptors have been identified [138, 139]. The functional unit composed of a and P subunits, and farmed as a pentamer which is permeable to Cl^- [34, 442]. Activation of the glycine receptor induces an increase in Cl" conductance and hyperpolarization of the neuron. Both glycine and $GABA_A$ receptor proteins exhibit a significant homology in sequence [359]. Barbiturates have also been shown to act on the glycine receptor a subunit, but with a smaller effect than that on the $GABA_A$ receptor [32]. In contrast to the $GABA_A$ receptor, the glycine receptor does not respond to most neurosteroids, except the water-soluble steroid, minaxolone [256]. Strychnine is an antagonist highly specific to the glycine receptor [77, 465]. Recently, Meier and Schmieden [309] reported that 2,3-dioxo-6-nitro-l,2,3,4-tetrahydrobenzoquinoxaline-7-sulfonamide, a potent AMPA receptor antagonist, also antagonizes glycine receptor activity. Glycine, strychnine, and 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzoquinoxaline-7-sulfonamide bind to the a subunit of the receptor [138, 140, 309], The glycine receptor has been found in the NGC/NMC, with a density that is much lower than that of the GABA receptor [15, 125, 380, 382,410].

3.3.2.2. Sensory Modulation

The role of glycine in sensory modulation has received little attention. No study examining the effect on sensory response of local infusion of glycine agonist into the NGC/NMC has been done. However, one study showed that microinjection of strychnine into the NMC did not change the latency of the tail-flick reflex [167], suggesting that glycine input does not generate a tonic inhibitory effect on algesic related neuronal activity.

3.3.2.3. Motor Modulation

No data exists on the effects of glycine agonist injection into the NGC/NMC on motor activity. However, it is thought that the NGC/NMC glycine system may be involved in phasic and tonic muscle activity. One study found that the injection of strychnine into the NGC/NMC generated myoclonus, indicating a NGC/NMC glycinergic mechanism is involved in myoclonus generation [68] (see details in the later section on myoclonus). It is speculated that motoneuron IPSPs induced by NGC/NMC stimulation are mediated by glycine, because IPSPs induced by NGC/NMC stimulation were blocked by iontophoretic application of strychnine [441].

3.3.2.4. Cardiovascular Modulation

Microinjection of glycine (50 nl) into the NMC of the rat produced an increase in mean arterial blood pressure in most cases, with a small number of injections inducing a decrease in blood pressure [487]. This suggests that a glycinergic mechanism in the NMC may play a role in the regulation of cardiovascular activity.

3.4. Dopamine

Dopamine has been implicated in a variety of physiological functions. Dopamine receptors are the major target of drug treatment in Parkinson's disease, restless leg syndrome, periodic leg movement disorder, Tourette syndrome, attention deficit hyperactivity disorder, schizophrenia and substance abuse. However, the functional aspects of

dopamine and dopamine receptors in the CNS remain unclear.

3.4.1. Dopamine Receptor

Dopamine receptors have been classified into two subtypes, dopamine D, and D_2. Recent studies demonstrated that additional dopamine receptors exist in the CNS. Dopamine D_5 receptors resemble the D_1 receptor, whereas D_3 and D_4 receptors are related to the D_2 receptor [10]. Thus, dopamine receptors can be segregated into two subfamilies, D_1- and D_2-like receptors.

Dopamine D_1- and D_2-like receptors produce opposite effects on adenylyl cyclase activity, which is typically increased by D_1like receptor stimulation, and decreased or unaltered by D_2-like receptor activation [221, 449, 500]. Dopamine D_1 and D_2-like receptors have differential affinity for dopamine agonists and antagonists. The dopamine D_1-like receptor can be both activated and antagonized by benzazepine derivatives, depending upon their molecular structures. SKF 38393 activates [190, 191], and SCH 23390 and SCH 39166 [66] inhibits dopamine D_1like receptor activity. The dopamine D_2-like receptor is activated by ergot alkaloids, quinpirole and bromocriptine [429], and inhibited by sulpiride and haloperidol [313, 408]. Many newer dopamine D_2-like receptor agonists and antagonists have been recently developed, that have a higher affinity for either the dopamine D_3 or D_4 receptor. The anti-parkinsonism drugs that have recently been approved in the United States, pramipexole and ropinirole, are dopamine D_3 receptor-preferring agonists [219, 313, 374]. Clozapine, an atypical anti-psychotic drug, is a D_4-receptor-preferring antagonist [486], that also acts on serotonergic and muscarinic receptors [310].

Both dopamine D_1 and D_2-like receptors are localized pre- and post-synaptically. Activation of the pre-synaptic dopamine D_1 [160, 322, 344] and D_2-like [232, 424] recep tors inhibits transmitter release. However, stimulation of the dopamine D_1like receptor resulted in an increase in trans mitter release has also been reported [53, 383]. Dopamine fibers and terminals have been identified in the NGC/NMC [228].

3.4.2. Sensory Modulation

Previous studies of dopamine function have been focused on the ventral midbrain dopaminergic neurons and their ascending projections to the basal ganglia. The descending dopamine system has received little attention. The effect of local dopamine agonist injection into the NGC/NMC on algesic response has not been studied, although one study showed that the dopamine D_2 receptor agonist, 2-(N-phenethyl-N-propyl) amino-5-hydroxytetralin HC1, injected into the raphe magnus in the amount of 2 µl, a relatively large amount allowing the chemical diffuse to the adjacent NMC, increases the latency of tail flick. In contrast, the dopamine D_1 receptor agonist, SKF 38393, failed to induce an antinociceptive response [373]. The effect of dopamine injection into the raphe magnus, and possibly the NMC, on algesic response could result from changes in NMC neuronal activity. Belczynski *et al.* [31] demonstrated that intra-peritoneal injection of cocaine, a dopamine uptake inhibitor, increases the NMC neuronal activity in response to somatic noxious stimulation. This cocaine effect on neuronal activity in the NMC can be partially reversed by chlorpromazine, a non-specific dopamine receptor antagonist, but not naloxone, I

3.4.3. Motor Modulation

The physiological function of dopamine in the NGC/NMC in regards to the regulation of motor activity has not been investigated. In our recent study, we found that microinjection of the dopamine D_2 receptor agonist, quinpirole, into the NMC suppresses neck, forelimb, genio-glossus and diaphragm EMG activity in decerebrate animals, In contrast, microinjection of SKF 38393 into the same, or nearby site of NMC had no effect on muscle activity [254], We have hypothesized that a glutamatergic mechanism may be involved in the dopamine D_2 receptor mediated muscle tone suppression. Activation of the dopamine D_2 receptor has been shown to inhibit NMDA receptor transmission [235, 265]. Our previous studies revealed that injection of NMDA into the NMC facilitates muscle activity [151, 247] (see details in Section *3.2.5)*. Thus, muscle tone suppression induced by the dopamine D_2 receptor agonist injected in the NMC may be mediated through an inhibition of NMDA receptor activity, which in turn disfacilitates motor activity.

3.5. **Norepinephrine**

Activation of the noradrenergic system has been reported to be involved in the modulation of motor activity [126, 244], waking [17], sympathetic activity [99] and nociception [209]. The noradrenergic system has been hypothesized to regulate the NGC/NMC region [176, 253].

3.5.7. *Adrenergic Receptor*

As early in 1948, Ahlquist [3] had reported that adrenergic receptors can be divided into 2 classes, a and P, based on pharmacological criteria. Both a- and ß-adrenoreceptors belong to the super family of G protein-coupled receptors.

3.5.1.1. α-A drenersic Receptor

Two subtypes, α_1 and α_2, of adrenergic receptor have been identified [86]. α_1-Adrenergic receptor can be activated by phenethylamines, such as norepinephrine, phenylephrine, and methoxamine. The α_2-Adrenergic receptor responds to imidazolines, such as clonidine and oxymetazoline.

α_1 Adrenergic receptors express differential affinity to WB-4101, an α_1 Adrenergic receptor antagonist. Morrow and Creese [328] revealed that one subtype of the α_1 adrenergic receptor, (A_{1A}, expresses high affinity, while the other subtype of the receptor, α_{1B}, has low affinity to WB-4101. It was subsequently reported that another subtype of α_1-Adrenergic receptor, α_{1c}, could be cloned from bovine brain [419]. At the cellular level, α_{1A}-adrenergic receptors are linked to the influx of extracellular calcium, whereas α_{1B}-adrenergic receptors are linked to the release of intracellular calcium [157].

α_2-Adrenergic receptors have been found to be activated by clonidine and antagonized by yohimbine. Four subtypes,

α_{2A}, α_{2B}, α_{2c} and α_{2D}, of α2-adrenergic receptor have been identified [40, 371, 437]. In the CNS, the pre-synpatic α_2-adrenoceptor is the α_{2A} subtype [271] which acts as an auto-or heteroreceptor [135].

3.5.1.1. ß-Adrenergilc Receptor

ß-Adrenergic receptors stimulate adenylate cyclase activity. Three subtypes, $ß_1$, $ß_2$, and $ß_3$, have been identified [105, 257]. Pharmacological studies showed that $ß_1$-adrenergic receptor expresses almost equal affinity to norepinephrine, whereas $ß_2$-adrenergic receptor displays a higher affinity for epinephrine than for norepinephrine [257].

3.5.2. Pain Modulation

Noradrenergic varicosities have been found to contact NMC neurons [312, 462J. Pharmacological studies demonstrated that injection of phentoiamine, an α_1/α_2-adrenoceptor antagonist, into the NMC produces hypoalgesia in the behaving animal [155]. In the pentobarbital anesthetized rat, norepinephrine and clonidine injected into the NMC produce analgesic response, which can be blocked by yohimbine but not WB-401, indicating an α_2-adrenoceptor mechanism is involved in hypoalgesia [161]. Noradrenergic induced analgesia may be mediated through an excitatory effect on On-cells in the NMC [168].

3.5.3. Motor Modulation

The effect of adrenergic receptor agonists and antagonists administered into the NGC/NMC on the motor system has not been studied. However, we had found that electrical stimulation in the NGC/NMC that produced muscle tone suppression simultaneously decreases in norepinephrine release onto motoneuron pools in the hypoglossal nucleus and spinal ventral horn in the decerebrate animal [253]. This result indicates that NGC/NMC stimulation-induced change in muscle tone may be partially medicated through an inhibition of the adrenergic system,

3.6. Serotonin

The serotonin (5-HT) system has been shown to involved in locomotion, sleep, mood, feeding and sympathetic activity. Activation of the pre-synaptic serotonin receptor, which serves as an auto- and heteroreceptor, produces an increase, a decrease, and no change in neurotransmitter release [25, 342]. On the other hand, the activation of post-synaptic 5-HT receptor elicited EPSPs, and increased neuronal activity of variety of neurons, such as motoneuron and cortical pyramidal neurons [2, 456, 484].

3.6.1. Serotonin Receptor

The classification of 5-HT receptors is based on the characterization of the structure, the binding affinity of agonist and antagonist, and physiological functions. Seven subfamilies of 5-HT receptor have been identified [505]. All 5-HT receptor subfamilies, except 5-HT_3, are related to adenylate cyclase activity *via G* proteins. 5-HT_3 receptors are Ca^{2+}-permeable ion channels. Most of 5-HT agonists and antagonists are not highly selective for 5-HT receptors [25]. They are also sensitive to adrenoreceptor and dopamine receptor [215, 511].

3.6.2. Physiological Functions of ***NGC/NMC-serotonin*** *System*

Some neurons in the NGC/NMC contain the 5-HT receptor [117, 324, 468], A serotonergic mechanism in the NGC/NMC has been shown to relate to sleep and nociception. Injection of 5-hydroxytryptophan, a serotonin precursor, into the NGC/NMC induced signs of slow wave sleep, including EEG synchronization and spindle and slow irregular activity in the hippocampus on the cat [260]. Using an *in vivo* dialysis technique, Blanco-Centurion and Salin-Pascual [39] found that serotonin levels in the NGC/NMC are low during SWS and lowest during REM sleep when compared with waking. With regard to nociception, serotonin micro injected into the NGC and the NMC did not alter the aigesic response [6]. However, unilateral injection of methysergide into the NGC/NMC significantly increased the current, necessary to inhibit the tail-flick reflex induced by stimulation from the contralaterai side [6], and reduced the amount of morphine required for PAG induced analgesia in the rat [224]. Using an *in vivo* dialysis technique, Taylor and Basbaum [464] found that the injection of formalin into the plantar surface of the hindlimb in the freely moving rat increased the serotonin level in the NMC. Lidocaine injected into the NMC also attenuated systemic serotonin injection induced analgesia [471]. These results indicated that serotonin in the NMC may also be involved in nociception.

3.7. Acetylcholine

The cholinergic system has been reportedly linked to learning, memory and motor activity. Dysfunction of the cholinergic system in the forebrain contributes to Alzheimer's disease and dementia.

3.7.1. Cholinergic Receptor

Cholinergic receptors are classified as nicotinic or muscarinic receptors. Nicotinic cholinergic receptors belong to the superfamily of receptor-gated ion channels, whereas muscarinic cholinergic receptors are members of the superfamily of G-protein-coupled receptors.

3.7.1.1. Nicotinic Receptor

Nicotinic receptors are located in the CNS and in muscle. The central (neuronal) and peripheral (muscle) nicotinic receptors are different in structure. The nicotinic receptor of the neuromuscular junction has 4 subunits, α, ß, γ, and δ, whereas the neurona! nicotinic receptor is composed of 2 subunits, a and (3 [166, 495, 503]. Highly selective nicotinic antagonists have been developed. α-Bungarotoxin is a peptide which blocks neuromuscular transmission without exhibiting any effect on the neuronal nicotinic receptor [217, 273]. In contrast, K-bungarotoxin is a highly selective neuronal nicotinic receptor antagonist [273, 276],

3.7.1.2. Muscarinic Receptor

Five cholinergic muscarinic receptors, M_1-M_5, have been identified. Cholinergic M_1, M_3, and M_5 receptors are coupled with phosphatidylinositol turnover, and enhance the

intracellular Ca^{2+} level, while the M_2 and M_4 receptors inhibit adenylyl cyclase activity [16, 259, 422]. Many muscarinic agonists and antagonists express a small degree of selectivity in relation to the subtypes of the receptor [24, 93]. In general, agonists tend to have higher potencies and an efficacy for M_2 and M_4 receptors [210, 306], whereas antagonists are more selective for the M_1 receptor than for the M_2 receptors [93].

3.*7.2. Sensory Modulation*

The NGC/NMC reticulospinal neurons include cholinergic and cholinoceptive neurons [177, 317, 360, 427]. The NGC/NMC neurons have both nicotinic and muscarinic receptors [75, 384, 443]. Consistent with anatomical findings, pharmacological studies showed that cholinergic agonists injected into the NGC/NMC induce antinociception [1, 196, 229]. Injection of the M_1 cholinergic receptor agonist, *(+)-cis*-methyldioxolane, into the NMC produces a dose-dependent increase in latency of hot-plate and tail-flick reflexes, which can be blocked by pre-treatment with the M_1 cholinergic receptor antagonist, pirenzepine, into the NMC [196]. It has been postulated that the MI cholinergic effect on algesic response is mediated through nitric oxide. Injection of the nitric oxide synthase inhibitor, $_L$-N^G-nitroarginine, into the NMC reversed (+)-cis-methyldioxolane-induced antinociception [196]. In contrast, $_L$-arginine pre-treatment reversed L-N -nitroarginine-induced antinociception produced by methyldioxolane injection [196]. The cholinergic M_2 receptor may also be involved in the modulation of algesic responses. Injection of methoctramine, a cholinergic M_2 receptor antagonist, into the NMC reversed PAG-morphine injection induced analgesic response in the tail-flick reflex test [445]. The nicotinic mechanism may also participate in algesic response. Spinella *et al.* [446] found that the injection of mecamylamine, a non-selective nicotinic receptor antagonist, into the NGC/NMC blocked PAG p-endorphin injection induced analgesia.

3.7.3. Motor Modulation

The NGC/NMC cholinergic system has no effect on basal muscle tone in the decerebrate cat [244]. However, the cholinergic system in the NGC/NMC is able to modulate motor activity if rhythmic peripheral sensory input is present. Kinjo *et al.* [226] reported that muscarinic cholinergic agonists, carbachol, methacholine, and arecoline, injected into the NMC in the decerebrate rat walking on the treadmill generated long-lasting (5-10 min) locomotion. This cholinergic injection induced locomotion can be blocked by pre-treatment with the cholinergic antagonist, atropine. In contrast, our study in the decerebrate animal found that acetylcholine microinjected into the nucleus paramedianus, an area adjacent and caudal to the NGC/NMC, produces muscle atonia [244]. The effect of acetylcholine on muscle activity could be reversed by prior injection of atropine.

3.7.4. Cardiovascular and Pulmonary Modulation

Acetylcholine injection into the NGC/NMC produced a significant decrease in mean arterial blood pressure, and a significant increase in heart rate in the decerebrate cat [246]. Cardiovascular changes induced by acetylcholine injection into the NGC/NMC could be blocked by a prior local injection of the muscarinic acetylcholine antagonist, atropine [246].

3.7.5. Regulation of Sleep

The cholinergic system in the NGC/NMC may be involved in the regulation of sleep. One study showed that carbachol injected into the NGC/NMC generated long lasting wakefulness and eliminated SWS and REM sleep [23].

3.8. Substance P

Substance P is a peptide which contains 11 amino acids. Substance P is a part of the tachykinin (neurokinin; NK) family, along with neurokinin A and neurokinin B [107], Substance P is found in the CNS and acts as a neurotransmitter [428]. Three types of tachykinin receptor, NK_1, NK_2, and NK_3, have been identified. NK_1, NK_2, and NK_3 receptors have preferential affinity to substance P, neurokinin A, and neurokinin B, respectively [389]. However, all three agonists can act on each of the three NK receptors [389]. The NK_1 receptor couples to G-proteins [401]. Activation of the NK_1 receptor activates phospholipase C, which in turn induces an increase in inositol 1,4,5-triphosphate and Ca^{2+} influx [320].

Substance P receptors have been identified in the NMC [282, 337]. Substance P immunoreactive fibers, which originate from the PAG [518] are found in the NMC. Pharmacological study has shown that injection of substance P into the NMC generates brief episodes of stepping activity (5-10 sec) with long latency (5-10 min) in the decerebrate rat [226]. Iontophoretic application of substance P into the NMC increased neuronal firing, which mimicked noxious stimuli (foot pinch) induced firing [150]. However, the nociceptive response was unaltered by application of substance P into the NMC [150].

3.9. Cholecystokinin

Cholecystokinin (CCK) is both a gut and a brain peptide. CCK is an 8 amino acid peptide, with immunoreactive fibers and terminals that have been found in the NMC [237, 439]. Two classes of CCK receptor, CCK_1 (CCK_A) and CCK, (CCK_B), have been identified. Both CCK_1 and CCK_2 receptors are coupled to G-proteins [377]. Activation of CCK_1 and CCK_2 receptors induced an efflux of Ca^{2+} [128, 476]. Although both CCK_1 and CCK_2 receptors are found in the brain, the CCK_1 receptor is mainly located in peripheral tissues [174]. The CCK_2 receptor has been shown to express an anti-opioid action [114]. Local infusion of CCK into the NMC facilitated algesic response to colon extension [124]. Although the tail flick latency was not altered, a significant inhibition of morphine-induced analgesia was found when CCK was infused into the NMC [171]. In contrast, a prior injection of CCK_2 receptor antagonist, L-365,260, into the NMC, potentiated morphine-induced analgesia [124].

3.10. Neurotensin

Neurotensin is a 13 amino acid peptide, with two subtypes of neurotensin receptor, NTS_1 and NTS_2. Both

NTS_1 and NTS_2 receptors belong to the superfamily of G-protein coupled receptor, and are sensitive to levocabastine, a histamine antagonist [301, 460, 494]. However, the two subtypes of receptor have differential affinities for neurotensin. NTS_1 is a high affinity receptor while the NTS_2 receptor is a low affinity receptor. The action of the NTS_1, but not the NTS_2, receptor can be blocked by the specific antagonist, SR48692 [143]. Studies using immunohistochemical and autoradiographical techniques have shown that neurotensin fibers [85] and neurotensin receptors [199, 222, 514] are localized in the NMC.

The NMC-neurotensin system is postulated to be involved in the regulation of the algesic response. Intra-cisternal infusion of neurotensin produces antinociception [72], Neurotensin-induced analgesia may be mediated through the PAG and the NMC. Neurotensin-containing neurons have been identified in the ventral PAG [29] and project to the NMC [267]. Injection of the neurotensin agonist, [$_D$-Trp^{11}]neurotensin, into the NMC potentiated PAG morphine-induced analgesia [479]. Microinjection of neurotensin into the NGC/NMC also elicits a dose-dependent increase in latency of tail-flick [111, 479] and hotplate reflex response [211]. Neurotensin microinjected into the NMC also inhibited visceral nociception, which can be attenuated by prior injections of the neurotensin antagonist, SR48692, into the NMC [481].

3.11. Hypocretin (Orexin)

Hypocretins (orexin) are newly discovered peptides, which are involved in the regulation of sleep-wake, motor activity, feeding, stress response, and autonomic activity. Hypocretin 1 (orexin A) and hypocretin 2 (orexin B) are derived from the same precursor, prepro-orexin [84, 406]. Hypocretin activates 2 G-protein coupled receptors, OX_1 and OX_2 [406]. Activation of OX_1 and OX_2 receptors induces an increase in cytoplasmic Ca^{++} and increases amino acid release [483].

In the CNS, hypocretinergic neurons were located exclusively in the posterior/lateral hypothalamus. Projecting fibers from hypocretinergic neurons have been found to be distributed in the widespread areas of the CNS, including the NGC/NMC [372]. Microinjection of orexin into the NGC and NMC produces an opposite effect on muscle activity, a decrease and increase in muscle tone, respectively [314].

3.12. Cannabinoid

Cannabinoids are psychoactive compounds obtained from the marijuana plant. Cannabinoids have been shown to have a profound effect on sensory perception, mood, and memory. These compounds may have therapeutic potential in the treatment of chronic pain. The endogenous cannabinoid ligands, anandamide and sn-2-arachidonylglycerol, were identified as an arachidonate derivative that activate the cannabinoid receptor [89, 118, 448]. Two subtypes of the cannabinoid receptor, CB_1 and CB_2, have been cloned and identified [297, 330]. Cannabinoid CB_1 and CB_2 receptors are found in the brain and peripheral tissues, but the cannabinoid CB_2 receptor is localized predominantly in peripheral tissues [129, 134, 280]. Activation of cannabinoid CB| receptor inhibits voltage-gated Ca^{2+} channels and activates K^+ channels [83, 118]. It has been shown that stimulation of the cannabinoid CB_1 receptor inhibits neurotransmitter release [90, 425].

Physiologically, microinjection of cannabinoid receptor agonists, WIN55,212-2 and HU210, into the NMC elicited a significant increase in tail-flick latency. This NMC cannabinoid effect on analgesic response can be attenuated by the co-administration of the cannabinoid receptor antagonist, SR141716A [295]. It has been hypothesized that antinociceptive response of cannabinoid injection into the NMC is mediated through inhibition of GABAergic transmission [488].

4. NGC/NMC AND NEUROLOGICAL DISEASES

As we described above, the NGC/NMC plays an important role in the modulation of sensory input and motor output. Thus, dysfunction of NGC/NMC could elicit sensory-motor disorders.

4.1. Neurodegenerative Diseases

Lewy bodies and Lewy neurites are neuronal inclusions, which are pathological features of several neurodegenerative diseases, such as Parkinsonism, REM sleep behavior disorder, Alzheimer's disease, and multiple system atrophy. Lewy bodies and Lewy neurites can be visualized using the hemotoxylin-eosin technique. Recent studies showed that a-synuclein is the major component of Lewy bodies and Lewy neurites. Thus, immunohistochemical staining for a-synuclein is better able to detect Lewy bodies and Lewy neurites than the hemotoxylin-eosin stain. Alpha-synuclein, which localizes in synaptic terminals [291] and binds to synaptic vesicles [79], is a hydrophilic molecule and a neuron-specific protein that consists of 140 amino acids. Physiologically, α-synuclein may play an important role in the maintenance and stabilization of fully mature synapses [331]. Abnormal aggregation of a-synuclein forms inclusion bodies, which are deposited in Lewy bodies and Lewy neurites [21].

4.1.1. Parkinson 's Disease (PD)

It is well-known that neurodegeneration in the ventral midbrain dopaminergic areas, the retrorubral nucleus (A8), the substantia nigra (A9), and the ventral tegmental area (A10), causes PD. Postmortem histology, using hemotoxylin-eosin technique, revealed that Lewy bodies and Lewy neurites are found in the ventral midbrain [121] and the NGC/NMC [153, 352] in Parkinson's disease patients. Using a-synuclein immunohistochemistry, Braak *et al.* [48, 49] reported that Lewy bodies and Lewy neurites are found in the NMC. Agyrophilic glial inclusions, so-called glial fibrillary tangles, are also found in the NGC/NMC in Parkinsonism [132, 175]. In a study on postencephalitic Parkinson patients, Geddes *et al.* [132] reported that neurofibrillary tangles were found in the NGC/NMC in 4 out of 7 patients. Animal studies have shown that Lewy bodies were found in the NGC/NMC in transgenic mouse expressing A53T human a-synuclein, which showed a severe movement disorder [133]. A53T human a-synuclein

has been shown to cause early onset of human Parkinsonism [133].

In recent studies, Braak *et al.* [49, 50] examined Lewy bodies in the CNS of PD-!ike patients at different stages, and concluded that neurodegeneration in the CNS in PD follows a predetermined sequence. They found that a-synuclein positive neurons are present in the olfactory bulb, locus coeruleus, and the NGC/NMC in the early stage of Parkinsonism. In contrast, neurons in the A8, A9, and A10 were normal in this early stage of Parkinsonism. In the advanced stages of PD, in which patients expressed the full range of symptoms, α-synuclein positive neurons were found in the locus coeruleus, NGC/NMC, and ventral midbrain dopaminergic areas. In the terminal stage of the PD, α-synuclein positive neurons were also found in the cortex. Thus, they concluded that the substantia nigra is not the induction site in the brain involved in the neurodegenerative process. Instead, the brainstem including the NGC/NMC, is one of the initial sites in the pathological process in PD [50].

4.1.2. REM Sleep Behavior Disorder (RBD)

REM sleep behavior disorder (RBD) is a movement disorder during sleep [415, 454]. RBD is characterized by violent and dream-enacting behavior during REM sleep [415]. A very high percent of RBD patients also have PD at the time of RBD diagnosis [103, 501]. It has been found that 38%-52% of RBD patients developed PD symptoms years after diagnosed [255, 358, 416,]. Eewy bodies have been found in the NMC of RBD patients, using a-synuclein immunohistochemical technique [478].

4.1.3. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis is a progressive neurodegenerative disease that affects both upper and lower motor neurons. Bunina bodies, the neuronal intracytoplasmic eosinophilic inclusions first described by Bunina [51], were found in lower motor neurons, including both cranial and spinal motoneurons. Recently, postmortem examination revealed that Bunina bodies are located in the NGC/NMC of amyotrophic lateral sclerosis patients [216, 335, 336, 354].

4.2. Other Neurological Diseases

4.2.1. Myoclonus (Including Restless Legs Syndrome and Periodic Leg Movement Disorder)

Myoclonus is a rapid, involuntary, muscle jerk. Periodic leg movement is myoclonus that appears regularly during sleep. Restless legs syndrome is an uncomfortable sensation in the legs and arms during rest. Restless legs syndrome typically appears in the late afternoon or evening. More than 80% of restless legs syndrome patients also have periodic leg movement.

Myoclonus can result from cancer as well as toxic, metabolic, infectious, and neurodegenerative disorders. The areas in the CNS involved in myoclonus include the cortex, thalamus, cerebellum, brainstem and spinal cord. The NGC/NMC has been suggested to be a myoclonus generator [87]. Postmortem examination revealed peri vascular lymphocytic cuffing in the cortex, cerebellum, basal ganglia, pons and medulla in opsoclonus-myoclonus patients [513], An increase in glucose metabolism in the NGC/NMC has been reported in human patients with palatal myoclonus [101]. Hyperactivity of the NGC/NMC mediated reflex myoclonus is reported in humans post-hypoxic myoclonus [152].

It has been suggested that toxic-induction of myoclonus results from reticular reflexes, and is mediated through the NGC/NMC. Patients with renal failure exhibit a variety of sensory-motor disorders, myoclonus [477] and restless legs syndrome [73, 395, 501, 504]. Chadwick and French [59] reported that uremic myoclonus closely resembles post-hypoxic myoclonus. They suggested that uremic myoclonus may be caused by the dysfunction of the NGC/NMC. Thus, myoclonus, including that of wakefulness and periodic leg movement during sleep, as well as restless legs, in renal failure patients may be mediated by the NGC/NMC. Indeed, animal studies demonstrated that systemic infusion of urea generated spontaneous and stimulus-sensitive myoclonus associated with paroxysmal activity in the NGC/NMC in the cat [332, 523]. A unit recording study revealed that neuronal activity in the NGC/NMC preceded urea-induced myoclonus in the rat [332]. A receptor binding assay study showed that urea inhibits strychnine binding in the NGC/NMC, indicating that urea may act on the NGC/NMC by the blockade of glycine transmission [69]. Not surprisingly, strychnine injection into the NGC/NMC did indeed elicit myoclonus in the rat [68]. Myoclonic jerks were also induced in human subjects when exposed to 1,1,1-trichloro-2,2-bis(/7-chlorophenyl) ethane [108]. Animal studies showed that local infusion *of p,p*[3]- l,l,l-trichIoro-2,2-bis(/?-chlorophenyl) ethane into the NGC/NMC generated stimulus-sensitive myoclonus in the rat [67, 70]. Injection of chloralose into the NGC/NMC also induced spontaneous and stimulus-sensitive myoclonus, indicating that NGC/NMC may play a role in the generation of myoclonus [11].

4.2,2. Narcolepsy-cataplexy

Cataplexy, the sudden loss of muscle tone during waking, triggered by emotional excitation, occurs in 0.05% of the population. Cataplexy can be provoked either by play or by the presentation of preferred foods in the narcoleptic dog [434]. Recent studies have shown that dysfunction of the hypocretin system in the hypothalamus is linked to narcolepsy [65, 272, 466]. However, neuronal dysfunction in the NGC/NMC may play a mediating role in the control of Cataplexy. Unit recording revealed that cataplexy-on and -off cells, which increase and decrease firing during calaplexic attack, respectively, are found in the NGC/NMC [434]. Cataplexy-on cells, which fire at high rates only during cataplexy and REM sleep, tend to be located in the NMC, whereas cataplexic-off cells, which fire in both waking and REM sleep, are found in the NGC [434].

5. CONCLUSION

Spontaneous and stimulus-induced involuntary muscle activities, such as tremor and myoclonus, have been hypothesized to originate from subcortical structures. The NGC/NMC has been suggested to be involved in sensory-motor disorders, largely because of its role in the regulation

of sensory-motor integration. Visceral and somatic sensory stimuli from widespread areas of the body converge on the NGC/NMC. Activation of the NGC/NMC, either by peripheral sensory stimuli or by the upper CNS stimulation, influences spinal dorsal horn sensory neuron activity. The NGC/NMC also serves as a final common pathway in the regulation of motor activity. Locomotion and muscle atonia can be induced by NGC/NMC activation. Because the NGC/NMC is a heterogeneous structure, neuronal dysfunction of sub-populations of the NGC/NMC neuron will cause specific sensory and motor abnormalities, rigidity, cataplexy and myoclonus. The balance between facilitatory and inhibitory systems in the NGC/NMC is critical to maintaining normal function of sensory and motor activity. The understanding of neurotransmitter and receptor types of NGC/NMC neurons, and their physiological functions in the regulation of sensory-motor integration, is of great importance in the design of therapeutic strategies to reverse some neurological disorders, such as Parkinson's disease, restless legs syndrome, periodic leg movement, REM sleep behavior disorder and cataplexy.

ABBREVIATIONS

AMPA	=	a-amino-3-hydroxy-5-methylisoxazolepropionic acid
APV	=	D(-)-2-amino-5-phosphonovalerate
CCK	=	Cholecystokinin
CNQX	=	6-cyano-7-nitroquinoxaline-2,3-dione
DGG	=	γ-D-glutamyglycine
DNQX	=	6,7-dinitroquinoxaline-2,3-dione
EEG	=	Electroencephalograph
EPSP	=	Excitatory postsynaptic potential
GDEE	=	$_{L}$-glutamic acid diethyl ester
mGluR	=	Metabotropic glutamate receptor
IPSP	=	Inhibitory postsynaptic potential
NGC	=	Nucleus gigantocellularis
NGCα and NGCv	=	Nucleus gigantocellularis alpha and ventralis respectively
NK	=	Neurokinin
NMC	=	Nucleus magnocellularis
NMDA	=	$_{N}$-methyl-D-aspartate
PAG	=	Periaqueductal gray
PD	=	Parkinson's disease
RBD	=	REM sleep behavior disorder
REM	=	Rapid eye movement
RMM	=	Rostral medial medulla
SWS	=	Slow wave sleep
5-HT	=	Serotonin

REFERENCES

[I] Abe, K., Kikuta, J., Kato, M., Ishida, K., Shigenaga, T., Taguchi, K., Miyatake, T. (2003) Effects of microinjected carbachoi on the antinociceptive response to noxious heat stimuli. *Biol. Pharm. Bull,* 26,162-165.

[2] Aghajanian, G.K., Marek, G.J. (1997) Serotonin induces excitatory postsynaptic potentials in apical dendrites of neocortical pyramidal cells. *Neuropharmacol, 4/5,* 589-600.

[3] Ahlquist, R.P. (1948) A study of the adrenergic receptors. *Am. J. Physiol.,* 153, 586-700.

[4] Aicher, S.A., Reis, D.J., Ruggiero, D.A., Milner, T.A. (1994) Anatomical characterization of a novel reticulospinal vasodeprcssor area in the rat medulla oblongata. *Neurosci.,* 60, 761-779.

[5] Aicher, S.A., Reis, D.J., Nicolae, R., Milner, T.A. (1995) Monosynaptic projections from the medullary gigantocellular reticular formation to sympathetic preganglionic neurons in the thoracic spinal cord. *J. Comp. Neurol,* 363, 563-580.

[6] Aimone, L.D., Gebhart, G.F. (1986) Stimulation-produced spinal inhibition from the midbrain in the rat is mediated by an excitatory amino acid neurotransmitter in the medial medulla. *J. Neurosci., 6,* 1803-1813.

[7] Akaike, A., Shibata, T., Satoh, M., Takagi, H. (1978) Analgesia induced by microinjection of morphine into and electrical stimulation of the nucleus reticularis paragigantocellularis of rat medulla oblongata. *Neuropharmacol,* 17, 775-778.

[8] Alderson, A.M., Downman, C.B.B. (1966) Supraspinal inhibition of thoracic reflexes of somatic and visceral origin. *Arch Hal. Biol.,* 104, 309-327.

[9] Alien, G.V., Cechetto, D.F. (1994) Serotoninergic and nonserotoninergic neurons in the medullary raphe system have axon collateral projections to autonomic and somatic cell groups in the medulla and spinal cord. *J. Com. Neurol.,* 350, 357-366.

[10] Andersen, P.H., Ginggrich, J.A., Bates, M.D., Dearry, A., Falardeau, P., Senogles, S.E., Caron, M.G. (1990) Dopamine receptor subtypes: beyond the D1/D2 classification. *TIPS* 11. 203-209.

[II] Angel, A. (1986) Animal models of myoclonus using 1,2-dihydroxybenzene (catechol) and chloralose. *Adv. Neurol.,* 43, 589-609.

[12] Antal, M. (1984) Termination areas of corticobulbar and corticospinal fibres in the rat. *J. Hirnforsch.,* 25, 647-659.

[13] Aoki, M., Mori, S. (1981) Locomotion elicited by pinna stimulation in the acute precollicular-postmammillary decerebrate cat. *Brain Res.,* 214, 424-428.

[14] Aprison, M.H., Daly, B.C. (1978) Biochemicals aspects of transmission at inhibitory synapses: the role of glycine. In: Agranoff, B.W., Aprison, M.H. Eds, Advances in neurochemistry 3. New York, Plenum, pp. 203-294.

[15] Araki, T., Yamano, M., Murakami, T., Wanaka, A., Betz, H., Tohyama, M. (1988) Localization of glycine receptors in the rat central nervous system: an immunohistochemical analysis using monoclonal antibody. *Neurosci.,* 25, 613-624.

[16] Ashkenazi, A., Peralta, E.G., Winslow, J.W., Ramachandran, J., Capon, D.J. (1989) Functionally distinct G proteins selectively couple different receptors to PI hydrolysis in the same cell. *Cell,* 56, 487-493.

[17] Aston-Jones, G., Bloom, F.E. (1981) Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *J. Neurosci.,* 1, 876-886.

[18] Atoji, Y., Watanabe, H., Yamamoto, Y., Suzuki, Y. (1995) Distribution of neurotensin-containing neurons in the central nervous system of the dog. *J. Comp. Neural.,* 353, 67-88.

[19] Ault, B., Evans, R.H., Francis, A.A., Oakes, D.J., Watkins, J.C. (1980) Selective depression of excitatory amino acid-induced depolarization by magnesium ions in isolated spinal cord preparations. *J. Physio/. (London),* 307, 413-428.

[20] Azami, J., Green, D.L., Roberts, M.H.T., Monhemius, R. (2001) The behavioural importance of dynamically activated descending inhibition from the nucleus reticularis gigantocellularis pars alpha. *Pain,* 92, 53-62.

[21] Baba, M., Nakajo, S., Tu, P.M., Tomita, T., Nakaya, K., Lee, V.M.Y., Trojanowski, J.Q., Iwatsubo, T. (1998) Aggregation of a-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies. *Am. J. Pathol.,* 152, 879-884.

[22] Bach, L.M.N. (1952) Relationships between bulbar respiratory, vasomotor and somatic facilitatory and inhibitory areas. *Am. J. Physio!.,* 171,417-435.
[23] Baghdoyan, H.A., Rodrigo-Angulo, M.L., McCarley, R.W., Hobson, J.A. (1984) Site-specific enhancement and suppression of desynchronized sleep signs following cholinergic stimulation of three brainstem regions. *Brain Res.,* 306, 39-52,
[24] Baker, R., MacLeod, A.M. (1993) Muscarinic agonists for the central nervous system. In: Kozikowski, A.P., Ed, Drug design for neuroscience. New York, Raven Press, pp. 61-85. [25] Barnes, KM., Sharp, T. (1999) A review of central 5-HT receptors and their function. *Neuropharmacol,* 38, 1083-1152.
[26] Basbaum, A.I., Clanlon, C.H., Fields, H.L. (1978) Three bulbospinal pathways from the rostral medulla of the cat: an autoradiographic study of pain modulating systems. *J. Comp. Neurol.,* 178,209-224.
[27] Basbaum, A,1., Fields, H.L. (1984) Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. *Ann. Rev. Neurosci, 7,* 309-338.
[28] Bederson, J.B., Fields, H.L., Barbaro, N.M. (1990) Hyperalgesia during naloxone-precipitated withdrawal from morphine is associated wilh increased On-cell activity in the rostral ventromediaf medulla. *Somatosensory Motor Res., 7,* 185-203.
[29] Behbehani, M.M. (1992) Physiological mechanisms of the analgesic effect of neurotcnsin. *Ann. NYAcad. Sci.,* 668, 253-265. [30] Behbehani, M.M., Pert, A. (1984) A mechanism for the analgesic effect of neurotensin as revealed by behavioral and electrophysiological techniques. *Brain Res.,* 324, 35-42.
[31} Belczynski, C.R. Jr., Pcrtovaara, A., Morrow, T.J., Cascy, K.L. (1990) The effect of systemic cocaine on the responses to noxious stimuli and spontaneous activity of medial bulboreticular projection neurons. *Brain Res.,* 527, 204-212.
[32] Belelli, D., Pistis, M., Peters, J.A., lambert, J.J. (1999) The interaction of general anaesthetics and neurosteroids with $GABA_A$ and glycine receptors. *Neurochetn. Int.,* 34, 447-452.
[33] Berman, A.L. (1968) The brain stem of the cat. Madison: Univ Wisconsin Press.
[34] Betz, H., Becker, C.M. (1988) The mammalian glycine receptor: biology and structure of a neuronal chloride channel protein. *Neurochem. Int..* 13, 137-146.
[35] Bharos, T.B., Kuypcrs, H.G.J.M., Lemon, R.N., Muir, R.B. (1981) Divergent collaterals from deep ccrcbellar neurons to thafamus and tectum, and to medulla oblongata and spinal cord: retrograde fluorescent and electrophysiological studies. *Exp. Brain Res.,* 42, 399-410. [36] Birch, P.J., Grossman, C.J., Haves, A.G. (1988) 6,7-dinitro-quinoxaline-2,3-dion and 6-nitro-7-cyano-quinoxaline-2,3-dion [60]] antagonise responses to NMDA in the rat spinal cord *via* an action at the strychnine-insensitive glycine receptor. *Eur. J. Pharmacol..* 156,177-180.
[37| Blair, R.W. (1985) Noxious cardiac input onto neurons in medullary reticular formation. *Brain Res,,* 326, 335-346. [38] Blair, R.W. (1987) Responses of feline medial medullary reticulospinal neurons to cardiac input. *J. Neurophysiol,* 58, 1149-1167. [39] Blanco-Centurion, C.A., Salin-Pascual, RJ. (2001) Extracellular serotonin levels in the medullary reticular formation during normal sleep and alter REM sleep deprivation. *Brain Res.,* 923, 128-136. [40] Blaxall, H.S., Murphy, T.J., Baker, J.C., Ray, C., Bylund, D.B. (1991) Characterization of the alpha-2C adrenergic receptor [64] subtype in the opossum kidney and in the OK cell line. *J. Pharmacol. Exp. Ther.,* 259, 323-329. [41] Blessing, W.W. (1990) Distribution of giutamate decarbosylasc-containing neurons in rabbit medulla oblongata with attention to intramcduilary and spinal projections. *Neurosci., 37,* 171-185,
[42] Bloom, F., fversen, L. (1971) Localizing ^{3}H-GABA in nerve terminals of rat cerebral cortex by electron microscopic autoradiography. *Nature,* 229, 628-630. [43] Borke, R.C., Nau, M.E., Ringier, R.L., Jr. (1983) Brain stem afferents of hypoglossal neurons in the rat. *Brain Res.,* 269, 47-55. [66]
[44] Bormann, J., Feigenspan, A. (1995) $GABA_C$ receptors. *TINS,* 18, 515-519. [45] Bowery, N.G., Hudson, A.L., Price, G.W. (1987) $GABA_A$ and GABAn receptor site dislribution in the rat central nervous system. *Neurosci.,* 20, 365-383.

Bowsher, D., Mallart, A., Petit, D., Albe-Fessard, D, (1968) A bulbar relay to the centre median. *J. Neurophysioi.,* 31, 288-300,

Braak, E., Sandmann-Keil, D., Rub, U., Gai, W.P., de Vos, R.A.1. Steur, E.N.H.J., Arai, K., Braak, H. (2001) a-synudein Jmmunopositive Parkinson's disease-related inclusion bodies in lower brain stem nuclei. *Ada Neuropathoi,* 101, 195-201.

Braak, H., Rub, U., Sandmann-Keil, D., Gai, W.P., de Vos, R.A.I.. Sleur, E.N.H.J., Arai, K., Braak, E. (2000) Parkinson's disease: affection of brain stem nuclei controlling premotor and motor neurons of the somatomotor system. *Ada Neuropaihol.* 99, 489-495.

Braak, H., del Tredici, K., Bratzke, H., Hamm-Clement, I.. Sandmann-Keil, D., Rub, U. (2002) Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages), *J. Neurol.,* 249, Suppl. 3, 1-5.

Braak, H., del Tredici, K., Rub, U., de Vos, R.A.I., Steur, E.N.HJ, Braak, H. (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging,* 24, 197-211,

Bunina, T.L. (i962) On intracellular inclusions in familial amyotrophic lateral sclerosis. *Korsakov J. Neuropathoi. Psychiat.* 62, 1293-1299.

Cameron, A.A., Khan, LA., Westlund, K.N., Willis, W.D. (1995) The efferent projections of the periaqucductal gray in the ra\t a *Phaseolus* vw/gara-Leuoagglutinin study. II. Descending projections. *J. Comp. Neural.,* 351, 585-601.

Cameron, D.L., Williams, J.T. (1993) Dopamine Dl receptors facilitate transmitter release. *Nature,* 366, 344-347,

Casey, K..L. (1969) Somatic stimuli, spinal pathways, and size of cutaneous fibers influencing unit activity in the medial medullary reticular formation, *Kxp. Neurol.,* 25, 35-56.

Casey, K.L. (1971) Responses of bulboreticular units to somalic stimuli eliciting escape behavior in the cat. *Int. J. Neurosci.,* 2, 15-28.

Casey, K.L. (1971) Escape elicited by bulboreticular stimulation in the cat. *Int. J. Neurosci.,* 2, 29-34,

Cassini, P., Ho, R.IL, Martin, G.F. (1989) The brainstem origin of enkephalin- and substance-P-like immunoreactive axons in the spinal cord of the North American opossum. *Brain Behav. Evol.* 34,212-222.

Cervero F., Wolstencroft, J.H. (1984) A positive feedback loop between spinal cord nociceptive pathways and antinociceptive areas of the cat's brain stem. *Pain,* 20, 125-338,

Chadwick, D., French, A.T. (1979) Uraemic myoclonus: an example of reticular reflex myoclonus? *J. Neurol. Neurosui'g. Psychial..* 42, 52-55.

Chai, C.Y., Wang, S.C, (1962) Localization of central cardiovascular control mechanism in lower brain stem of the cal *Am. J. Physiol.,* 202, 25-30.

Chai, C.Y., Lin, Y.F., Lin, A.M.Y., Pan, C.M,, Lee, E.H.Y., Kuo. J.S, (1988) Existence of a powerful inhibitory mechanism in the medial region of caudal medulla - with special reference to ihe paramcdian reticular nucleus. *Brain Res. Bull,* 20, 515-528.

Chapman, C.D., Ammons. W.S., Foreman, R.D. (1985) Raphe magnus inhibition of feline T,-T_4 spinoreticular tract eel! responses to visceral and somatic inputs. *J. Neurophysioi.,* 53, 773-785.

Chase, M.H., Enomoto, S., Murakami, T,, Nakamura. Y., Taira, M (1981) Intraeellular potential of medullary reticular neurons during sleep and wakefulncss. *Exp. Neurol.,* 71, 226-233.

Chase, M.H., Morales, F.R., Boxer, P.A., Fung, S.J., Soja, P.]. (1986) Effect of stimulation of the nucleus relicularis gigantocellularis on the membrane potential of cat lumbar motoneurons during steep and wakefulness. *Brain Res.,* 386. 237-244.

Chemelli, R.M., Willie, J.T., Sinton, C.M., Elmquist, J.K., Scammell, T., Lee, C., Richardson, J.A., Williams, S.C., Filch, T.H., Saper, C.B., Yanagisawa, M. (1999) Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell,* 98, 437-451.

Chipkin, R.E,, lorio, L.C., Coffin, V.C., McQuade, R.D., Berger, J.G., Barnelt, A. (1988) Pharmacological profile of SCH 39166: a dopamine Dl selective benzonaphthazepine with potential antipsychotic activity. *J. Pharmacol. Exp. Ther.,* 247, 1093-1102.

Chung, E.Y., Van Wocrt, M.H, (1984) DDT myoclonus: sites and mechanism of action. *Exp. Neurol,* 85, 273-282,

[68] Chung, E., Yocca, F., Van Woert, M.H. (1985) Urea-induced myoclonus: medullary glycine antagonism as mechanism of action. *LifeSci.,* 36, 1051-1058.
[69] Chung, E.Y., Van Woert, M.H. (1986) Urea myoclonus: possible involvement of glycine. *Adv. Neural.,* 43, 565-568.
[70] Chung, E.Y., Van Woert, M.H. (1986) DOT myoclonus: site of "myoclonus center" in the brain. *Adv. Neural.,* 43, 569-575.
[71] Ciriello, J., Caverson, M.M., Calaresu, F.R., Krukoff, T.L. (1988) Neuropeptide and serotonin immunoreactive neurons in the cat ventrolateral medulla. *Brain Res.,* 440, 53-66.
[72] Clineschmidt, B.V., McGuffin, J.C. (1977) Neurotensin administered intracisternally inhibits responsiveness of mice to noxious stimuli. *Eur. J. Pharmacol.,* 46, 395-396.
[73] Collado-Seidel, V., Kohnen, R., Samtleben, W., Hillebrand, G.F., Oertel, W.H., Trenkwalder, C. (1998) Clinical and biochemical findings in uremic patients with and without restless legs syndrome. *Am. J. Kidney Dis.,* 31, 324-328.
[74] Commons, K.G., Aicher, S.A., Kow, L.M., Pfaff, D.W. (2000) Presynaptic and postsynaptic relations of (j.-opioid receptors to 7-aminobutyric acid-immunoreactive and medullary-projecting periaqueductal gray neurons. *J. Comp. Neurol.,* 419, 532-542.
[75] Cortes, R., Probst, A., Palacios, J.M. (1984) Quantitative light microscopic autoradiographic localization of cholinergic muscarinic receptors in the human brain: brainstem. *Neurosci.,* 12, 1003-1026.
[76] Curtis, D.R., Phillis, J.W., Watkins, J.C. (1959) Chemical excitation of spinal neurons. *Nature,* 183, 611-612.
[77] Curtis, D.R., Duggan, A.W., Johnson, G.A.R. (1971) The specificity of strychnine as a glycine antagonist in the mammalian spinal cord. *Exp. Brain Res.,* 12, 547-565.
[78] Curtis, D.R., Duggan, A.W., Felix, D., Johnson, G.A.R., Tebecis, A.K., Watkins, J.C. (1972) Excitation of mammalian central neurons by acidic amino acids. *Brain Res.,* 41, 283-301.
[79] Davidson, W.S., Jonas, A., Clayton, D.F., George, J.M. (1998) Stabilization of a-synuclein secondary structure upon binding to synthetic membrane. *J. Bio/. Chem.*. 273, 9443-9449.
[80] Davies, J., Watkin, J.C. (1979) Selective antagonism of amino acid-induced and synaptic events in the cat spinal cord. *J. Physiol., (London),* 297,621-635.
[81] Davies, J., Evans, R.H., Jones, A.W., Smith, D.A.S., Watkin, J.C. (1982) Differential activation and blockade of excitatory amino acid receptors in the mammalian and amphibian central nervous system. *Comp. Biochem. Physiol.,* 72C, 211-224.
[82] Davies, J., Watkin, J.C. (1982) Actions of D and L forms of 2-amino-5-phosphonovalerate and 2-amino-4-phosphonobutyrate in the cat spinal cord. *Brain Res.,* 206, 172-177.
[83] Deadwyler, S.A., Hampson, R.E., Bennett, B.A., Edwards, T.A., Mu, J., Pacheco, M.A., Ward, S.J., Childers, S.R. (1993) Cannabinoids modulate potassium current in cultured hippocampal *neurons. Receptors Channel,* 1, 121-134.
[84] De Lecea, L., Kilduff, T.S., Peyron, C., Gao, X.B., Foye, P.E., Danielson, P.E., Fukuhara, C., Battemberg, E.L.F., Gautvik, V.T., Bartlett, F.S., Frankel, W.N., van Den Pol, A.N., Bloom, F.E., Gautvik, K.M., Sutcliffe, J.G. (1998) The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proc. Nail. Acad. Sci. USA,* 95, 322-327.
[85] De Leon, M., Covenas, R., Anrvaez, J.A., Tramu, G., Aguirre, J.A., Gonzalez-Baron, S. (1991) Distribution of neurotensin-like immunoreactive cell bodies and fibers in the brainstem of the adult male cat. *Peptides.* 12, 1201-1209.
[86] Delbarre, B., Schmitt, H. (1973) A further attempt to characterize sedative receptors activated by clonidine in chickens and mice. *Eur. J. Pharmacol.,* 22, 355-359.
[87] Denny-Brown, D. (1968) Quelques aspects physiologiques des myoclonies. In: Bonduelle, M., Gastaut, H. Eds, Les myoclonies. Paris, France, Masson. pp.121-129.
[88] DePaoli, A.M., Hurley, K.M., Yasada, K., Reisine, T., Bell, G. (1994) Distribution of K opioid receptor mRNA in adult mouse brain: an *in situ* hybridization histochemistry study. *Mole. Cell Neurosci.,* 5, 327-335.
[89] Devane, W.A., Hanus, L., Breuer, A., Pertwee, R.G., Stevenson, L.A., Griffin, G., Gibson, D., Mandelbaum, A., Etinger, A., Mechoulam, R. (1992) Isolation and structure of a brain constituent that binds to cannabinoid receptor. *Science,* 258, 1882-1884.
[90]
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[100]
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[110]
[112]

Diana, M.A., Levenes, C., Mackie, K., Marty, A. (2002) Short-term retrograde inhibition of GABAergic synaptic currents in rat Purkinje cells is mediated by endogenous cannabinoids. ./. *Neurosci.,* 22, 200-208.
Dickenson, A.H., Oliveras, J.L., Besson, J.M. (1979) Role of the nucleus raphe magnus in opiate analgesia as studied by the microinjection technique in the rat. *Brain Res.,* 170, 95-111. Ding, Y.Q., Kaneko, T., Nomura, S., Mizuno, N. (1996) Immunohistochemical localization of |a-opioid receptors in the central nervous system of the rat. *J. Comp. Neural.,* 367, 375-402. Dorje, F., Wess, J., Lainbrecht, G., Tacke, R., Mutschler, E., Brann, M.R. (1991) Antagonist binding profiles of five cloned human muscarinic receptor subtypes. *J, Pharmacol. Exp. Ther.,* 256, 727-733.
Dostrovsky, J.O. (1984) Brainstem influences on transmission of somatosensory information in the spinocervicothalamic pathway. *Brain Res.,* 292, 229-238.
Dostrovsky, J.O., Guilbard, G. (1990) Nociceptive responses in medial thalamus of the normal and arthritic rat. *Pain,* 40, 93-104. Drew, T., Rossignol, S. (1990) Functional organization within the medullary reticular formation of intact unanesthetized cat. 1. Movement evoked by microstimulation. *J. Neurophysiol.,* 64, 767-781.
Drew, T., Rossignol, S. (1990) Functional organization within the medullary reticular formation of intact unanesthetized cat. II. Electromyographic activity evoked by microstimulation. *J. Neurophysiol,* 64, 782-795.
Drew, T., Cabana, T., Rossignol, S. (1996) Responses of medullary reticulospinal neurons to stimulation of cutaneous limb nerves during locomotion in intact cats. *Exp. Brain Res.,* 111, 153-168. Drolet, G., Gauthier, P. (1985) Peripheral and central mechanisms of the pressor response elicited by stimulation of the locus coeruleus in the rat. *Can. J. Physiol. Pharmacol.,* 63, 599-605. Drawer, E.J., Hammond, D.L. (1988) GABAergic modulation of nociceptive threshold: effects of THIP and bicuculline microinjected in the ventral medulla of the rat. *Brain Res.,* 450, 316-324.
Dubinsky, R.M., Hallett, M., Di Chiro, G., Fulham, M., Schwankhaus, J. (1991) Increased glucose metabolism in the medulla of patients with palatal myoclonus. *Neurology,* 41, 557-562. Eccles, J.C., Nicoll, R.A., Schwarz, D.W.F., Taborikova, H., Willey, T.J. (1976) Medial reticular and perihypoglossal neurons projecting to cerebellum. *J. Neurophysiol.,* 39, 102-108. Eisensehr, I., Lindeiner, IT., Jager, M., Noachtar, S. (2001) REM sleep behavior in sleep-disordered patients with versus without Parkinson's disease: is there a need for polysomnography? *J. Neural Sci.,* 186,7-11.
Ellenberger, H.H. (1999) Distribution of bulbospinal y-aminobutyric acid-synthesizing neurons of the ventral respiratory group of the rat. *J. Comp. Neurol,* 411, 130-144. Emorine, L.J., Marullo, S., Briend-Sutren, M.M., Patey, G., Tate, K., Delavier-Kiutchko, C., Strosberg, A.D. (1989) Molecular characterization of the human (3,-adrenergic receptor. *Science,* 245, 1118-1121.
Engberg, I., Lundberg, A., Ryall, R.W. (1968) Reticulospinal inhibition of transmission in reflex pathways. *J. Physiol. (London),* 194,201-223.
Erspamer, V. (1983) Amphibian skin peptides in mammals -looking ahead. *TINS,* 6, 200-201.
Eskenasy, J.J. (1972) Status epilepticus by dichlorodiphenyltrichlo-rethane and hexachlorcyclohexane poisoning. *Rev. Roum. Neurol, 6,* 435-442.
Evans, R.H., Francis, A.A., Watkin, J.C. (1978) Mg^{2+} like selective antagonism of excitatory amino acid-induced responses by a, E-diaminopimelic acid, D-a-aminoadipate and HA-966 in isolated spinal cord of frog and immature rat. *Brain Res.,* 148, 536-542. Evans, R.H., Francis, A.A., Hunt, K., Oakes, D.J., Watkin, J.C. (1982) The effects of a series of w-phosphonic o-carboxylic amino acids on electrically evoked and amino acid induced responses in isolated spinal cord preparations. *Br. J. Pharmacol,* 75, 65-75. Fang, F.G., Moreau, J.L., Fields, H.L. (1987) Dose-dependent antinociceptive action of neurotensin microinjecled into the rostroventromedial medulla of the rat. *Brain Res.,* 420, 171-174. Fang, F.G., Haws, C.M., Drasner, K., Williamson, A., Fields, H.L. (1989) Opioid peptides (DAGO-enkephalin, dynorphin A(1-13),

[193] Isa, T., Sasaki, S. (1992) Mono- and disynaptic pathways from Forei's field H to dorsal neck motoneurones in the cat, *Exp. Brain Res.,* 88, 580-593.

[194] Ito, H., Hasegawa, T.. Shoin, .1., Yamamoto, S., Kitsukawa, H. (!986) Ascending fibers from the gigantocellular nucleus to the centromcdian nucleus of the thalamus in cats. *Jpn. J. Physiol.,* 36, 723-732.

[195] Iwakiri, H., Oka, T., Takakusaki, K., Mori, S. (1995) Stimulus effects of the medial pontinc reticnlar formation and the mesencephalic locomotor region upon medullary reticulospinal neurons in acute decerehrate cats. *Neurosci. Res.,* 23, 47-53.

[196] Iwamoto, E.T., Marion, L. (1994) Pharmacological evidence that nitric oxide mediates the anlinociceplion produced by muscarinic agonists in the rostral ventral medulla of rats. *J. Pharmacol. Exp. Ther-.,* 269,699-708.

[197] Jankowska, E., Lund, S., Lundberg, A., Pompeiano, O. (1968) Inhibitory effects evoked through ventral reticulospinal pathways. *ArchltalBioL,* 106, 124-140.

[198] Jeljcli, M., Strazielle, C., Caston, J., Lalonde, R. (2000) Effects of centrolateral or medial thalamic lesions on motor coordination and spatial orientalion in rats. *Neurosci. Res.,* 38, 155-164,

[199] Jcnnes, L., Stumpf, W.E., Kalivas, P.W, (1982) Neurotcnsin: topographical distribution in rat brain by immunochemistry. *J. Comp. Neurol.,* 210, 211-224.

[200] Jensen, T.S., Yaksh, T.L. (1986) 1. Comparison of antinociceptive action of morphine in the periaqueductal gray, medial and paramedial medulla in rat. *Brain Res.,* 363. 99-113.

[201] Jensen, T.S., Yaksh, T.L. (1989) Comparison of the antinociceptive effect of morphine and glutamate at coincidental sites in the periaqueductal gray and medial medulla in the rat. *Brain Res.,* 476, 1-9.

[202] Johansson, J.N., Hokfelt, T., Pernow, B., Jeffcoate, S.L., White, H, Stenbusch, H.W.M., Verhofstad, A.A.J., Emson, P.C., Spindel, E. (1981) Immunohistochemical support for three putative transmitters in one neuron: coexistence of 5-hydroxytryptamine, substance P- and thyrotropin releasing hormone-like immunoreactivity in medullary neurons projecting to the spinal cord. *Neurosci.,* 8, 1857-1881.

[203] Johnson, J.W., Ascher, P. (1987) Glycine potentiates the NMDA response in cultured mouse brain neurons. *Nature,* 325, 529-531.

[204] Jones, A.W., Smith, D.A.S., Watkins, J.C. (1984) Structure-activity relations of ciipeptidc antagonists of excitatory amino acids. *Neurosci.,* 13,573-581.

[205] Jones, B.E. (1990) Immunohistochemical study ofcholine acetyltransferase-immunoreactive processes and cells innervating the pontomedullary reticular formation in the rat. *J. Comp. Neural.* 295,485-514.

[206] Jones, B.E., Yang, T.Z. (1985) The efferent projections from the reticular formation and the locus coeruleus studies by anterograde and retrograde axona! transport in the rat. *J. Comp. Neural..* 242, 56-92.

[207] Jones, B.E., Pare, M., Beaudet, A. (1986) Retrograde labeling of neurons in the brain stem following injections of [^{1}HJcholine into the rat spinal cord. *Neurosci.,* 18, 901-916.

[208] Jones, B.E., Beaudet, A. (1987) Distribution of acetylcholine and catecholaminc neurons in the cat brain stem: a choline acetyltransferase and tyrosine hydroxylase immunohistochemical study../, *Comp. NeuroL,* 261, 15-32.

[209] Jones, S.L., Gebhart, G.F. (1986) Quantitative characterization of coerulcospinal inhibition of nociceptive transmission in the rat. *J. Neurophysiol.,* 56, 1397-1410.

[210J Jones, S.V.P., tevey, A.I., Wciner, D.M., Ellis, J., Novotny, E., Yu, S.H., Dorjc, F., Wess, J., Brann, M.R. (1992) Muscarinic acetylcholine receptors. In: Brann, M.R. (Ed), Molecular biology of G-protcin-coupled receptors. Boston, Birkhauser. pp. 170-197.

[211] Kalivas, P.W., Jennes, L., Nemeroff, C.B., Prange, A.R., Jr. (1982) Ncurotensin: topographical distribution of brain sites involved in hypothermia and antinociccption. *J. Comp. NeuroL,* 210, 225-238,

[212] Kalyuzhny, A.E., Arvidsson, U., Wu, W., Wessendorf, M.W. (1996) u.-Opioid and 8-opioid receptors are expressed in brainstem antinociceptive circuits: studies using immunocytochemistry and retrograde tract tracing. *J. Neurosci.,* 15, 6490-6503.

[213] Kalyuzhny, A.E., Wessendorf, M.W. (1998) Relationship of u.- and 5-opioid receptors to GABAergic neurons in the central nervous

system, including antinociceptive brainstem circuits. *J.* 0«;i. *Neurol.,* 392, 528-547.
Kanamori, N., Sakai, K., Jouvet, M. (1980) Neuronal aciivif. specific to paradoxical sleep in the ventromedial mediilSarv reticular formation of unrestrained cats. *Brain Res.,* 189, 251-25?
Kapur, S., Zipursky, R.B., Remington, G., Jones, C., DaSilva, .1. Wilson, A.A., Houle, S. (1998) 5-HT2 and D2 receptor occupancy of olanzapine in schizophrenia: a PET investigation. *Am. j. Pshcyiat.,* **155,** 921-928.
Kato, S., Hirano, A. (1992) Involvement of the brain stem relieular formation in familial amyotrophic lateral sclerosis. *Chn. Neufopathol.,* 11,41-44.
Katz, B., Miledi, R. (1978) A re-examination of curare action at HIE motor end plate. *Proc. R. Soc. Loud B,* 203, 119-133.
Kausz, M. (1991) Arrangement of neurons in the medullary reticular formation and raphc nuclei projecting to thoracic, lumbar . and sacral segments of the spinal cord in the cat. *Anat. Embijol.,* 183,151-163.
Kaye, C.M., Nicholls, B. (2000) Clinical pliarmacokiiictics of ropinirole. *Clin. Pharmacokinet., 39,* 243-254.
Keizer, K., Kuypers, H.G.J.M. (1984) Distribution of corticospmal neurons with collaterals to lower brain stem reticular formation in cat. *Exp. BrairiRes.,* 54, 107-120.
Kelly, E., Willocks, A.L., Nahorski, S.R. (1987) Neurochcmical and behavioral evidence that dopamine D-2 receptors in striatiim couple to the Ni regulatory protein and inhibition of cyclic AMP accumulation. *Naunyn-Schmiedeberg's Arch PharmucoL,* 335, 618-623.
Kessler, J.P., Moyse, *E..,* Kitabgi, P., Vincent, J.P., Beaudel. .A (1987) Distribution of neurotensin binding sites in the caudal brainstem of the rat: a light microscopic radioautographic study. *Neurosci.,23,* 189-198.
Kessler, M., Terramani, T., Lynch, G., Baudry, M. (1989) A glycine site associated with N-methyl-D-aspartic acid receptors: characterization and identification of a new class of antagonists. J, *Neurochem.,* 52, 1319-1328.
Kiefel, J.M., Cooper, M.L., Bodnar, R.J. (1991) Inhibition of mesencephalic morphine analgesia by methyscrgide in the medial ventral medulla of rats. *Physio/. Behav.,* 51, 201-205.
Kim, S.J., Calejesan, A.A., Zhuo, M. (2002) Activation of brainstem metabotropic glutamate receptors inhibits spinal nociception in adult rats *Pharmacol. Biochem Behav.*. 73. 429-437.
Kinjo, N., Atsuta, Y., Webber, M., Kyle, R., Skinner, R.D.. Garcia-Rill, E. (1990) Medioventral medulla-induced locomotion. *Brain Res. Bu/!.. 24, 509-516*.
Kinomura, S., Larsson, J,, Gulyas, B., Roland, P.E. (1996) Activation by attention of the human reticular formation and thalamic intralaminar nuclei. *Science,* 271, 512-515.
Kitahama, K., Nagatsu, I., Geffard, M., Macda, T. (2000) Distribution of dopamine-immunoreactive fibers in the rat brainstem. J. *Chem. Neuroanat.,* 18, 1-9.
Klamt, J.G., Prado, W.A. (1991) Antiiiociception and behavioral changes induced by carbachol microinjected into identified sites of the rat brain. *Brain Res.,* 549, 9-18.
Kleckner, N.W., Dinglcdine, R. (1988) Requirement for glycine in activation of NMDA receptors expressed in *Xenopus* oocytes. *Science,* 241,835-837.
Kodama, T., Lai, Y.Y., Siegel, J.M (1998) Enhanced glutamate release during REM sleep in the rostromedial medulla as measured by *in vivo* microdialysis. *Brain Res.,* 780, 178-181.
Koga, E., Momiyama, T. (2000) Presynaptic dopamine D.-like receptors inhibit excitatory transmission onto rat ventral legniemal dopamincrgic neurones. *J. Physio/ (Lone/on),* 523, 163-173.
Kohyama, J., Lai, Y.Y., Siegel, J.M. (1998) Reticulospinal systems mediate atonia with short and long latencies. *J. Neurophysiol..* 80, 1839-1851.
Kostarczyk, E., Zhang, X., Giesler, G.J. Jr. (1997) Spinohypothalamic tract neurons in the cervical enlargement of rats: locations of antidromically identified ascending axons and their collateral branches in the contralatera! brain. *J. Neumphvsiol.,* 77,435-451.
Kotecha, S.A., Oak, J.N., Jackson, M.F., Percz, Y., Orser, B.A., Van Tol, H.H.M., McDonald, J.F. (2002) A D2 class dopamine

receptor transactivates a receptor tyrosine kinase to inhibit NMDA receptor transmission. *Neuron,* 35, 1111-1122.

[236] Krout, K.E., Belzer, R.E., Loewy, A.D. (2002) Brainstem projections to midline and intralaminar thalamic nuclei of the rat. *J. Comp. Neural.,* 448, 53-101.

[237] Kubota, Y., Inagaki, S., Shiosaka, S., Cho, H.J., Tateishi, K., Hashimura, E., Hamaoka, T., Tohyama, M (1983) The distribution of cholecystokinin octapeptide-like structures in the lower brain ,'t-stem of the rat: an immunohistochemical analysis. *Neurosci., 9,* 587-604.

[238] Kuo, J.S., Hwa, Y., Chai, C.Y. (1979) Cardio-inhibitory mechanism in the gigantocellular reticular nucleus of the medulla oblongata. *Brain Res.,* 178, 221-232.

[239] Kutsuwada, T., Kasiwabuchi, N., Mori, H., Sakimura, K.., Kushiya, E., Araki, K., Meguro, H., Masaki, H., Kumanishi, T., Arakawa, M., Mishina, M. (1992) Molecular diversity of the NMDA receptor channel. *Nature,* 358, 36-41.

[240] Kuypers, H.G.J.M. (1958) An anatomical analysis of cortico-bulbar connexions to the pons and lower brain stem in the cat. *J. Anal.,* 92, 198-218.

[241] Kuypers, H.G.J.M., Maisky, V.A. (1975) Retrograde axonal transport of horseradish peroxidase from spinal cord to brain stem cell groups in the cat. *Neurosci. Lett.,* 1, 9-14.

[242] Kwiat, G.C., Basbaum, A.I. (1992) The origin of brainstem noradrenergic and serotonergic projections to the spinal cord dorsal horn in the rat. *Somatosensory Motor Res.,* 9, 157-173.

[243] Lai, Y.Y., Siegel, J.M., Wilson, W.J. (1987) Effect of blood pressure on medial medulla-induced muscle atonia. *Am. J. Physioi,* 252.H1249-H1257.

[244] Lai, Y.Y., Siegel, J.M. (1988) Medullary regions mediating atonia. *J. Neurosci.,* 8, 4790-4796.

[245] Lai, Y.Y., Strahlendorf, H.K., Fung, S.J., Barnes, C.D. (1989) The actions of two monoamines on spinal motoneurons from stimulation of the locus coeruleus in the cat. *Brain Res.,* 484, 268-272.

[246] Lai, Y.Y., Siege], J.M. (1990) Cardiovascular and muscle tone changes produced by microinjection of cholinergic and glutamatergic agonists in dorsolateral pons and medial medulla. *Brain Res.,* 514,27-36.

[247] Lai, Y.Y., Siegel, J.M. (1991) Pontomedullary glutamale receptors mediating locomotion and muscle tone suppression. *J. Neurosci.,* 11,2931-2937.

[248] Lai, Y.Y., Wu, J.P., Kuo, J.S., Siegel, J.M. (1995) Distribution of NMDA and kainate receptors in the pontine and medullary atonia-related regions. *Sleep Res.,* 24A, 38.

[249] Lai, Y.Y., Wu, J.P., Kuo, J.S., Siegel, J.M. (1996) Co-localization of NMDA and non-NMDA receptors in the neurons of rostra] ventromedial medulla. *Soc. Neurosci. Abstr.,* 22, 1994.

[250] Lai, Y.Y., Siegel, J.M. (1997) Brainstem-mediated locomotion and myoclonic jerks. I. Neural substrates. *Brain Res.,* 745, 257-264.

[251] Lai, Y.Y., Siegel, J.M. (1997) Brainstem-mediated locomotion and myoclonic jerks. II. Pharmacological effects. *Brain Res.,* 745, 265-270.

[252] Lai, Y.Y., Clements, J.R., Wu, X.Y., Shalita, T., Wu, J.P., Kuo, J.S., Siegel, J.M. (1999) Brainstem projections to the ventromedial medulla in cat: A retrograde transport horseradish peroxidase and immunohistochemical studies. *J. Comp. Neural,* 408, 419-436.

[253] Lai, Y.Y., Kodama, T., Siegel, J.M. (2000) Monoamine release in medial medulla-induced muscle tone suppression: an *in vivo* dialysis study. *Sleep,* 23, A3.

[254] Lai, Y.Y., Kodama, T., Siegel, J.M. (2003) Differential effect of activation of nuclei gigantocellularis and magnocellularis on respiratory activity. *Soc. Neurosci. Abstr. Vol.* 29.

[255] Lai, Y.Y., Siegel, J.M. (2003) Physiological and anatomical link between Parkinson-like disease and REM sleep behavior disorder. *Mot. Neurobiol.,* 27, 137-151.

[256] Lambert, J.J., Belelli, D., Shepherd, S.E., Pistis, M., Peters, J.A. (1999) The selective interaction of neurosteroids with the GABAA receptor. In: Baulieu, E.E., Robel, P., Schumacher, M. Eds, Contemporary endocrinology: a new regulatory function in the nervous system. Totowa, NJ, Humana Press, pp. 125-142.

[257] Lands, A.M., Arnold, A., McAuliff, J.P., Luduena, P.P., Brown, T.G. Jr. (1967) Differentiation of receptor systems activated by sympathomimetic amines. *Nature,* 214, 597-598.

[258] Largent, B.L., Wikstrom, H., Gundlach, A.L., Snyder, S.H. (1987) Structural determinants of sigma receptor affinity. *Mo/. Pharmacol,* 32, 772-784.

[259] Lechleiter, J., Peralta, E., Clapham, D. (1989) Diverse functions of muscarinic acetylcholine receptor subtypes. *TIPS,* Suppl, 34-38.

[260] Ledebur, I.X., Tissot, R. (1966) Modification de I'activite electrique cerebrale chez le Lapin sous l'effect de microinjections de precurseurs des monoamines dans les structures somnogenes bulbaires et pontiques. *EEC Clin. Neurophysiol.,* 20, 370-381. Leger, L., Wiklund, L. (1982) Distribution and numbers of indoleamine cell bodies in the cat brainstem determined with Falck-Hillarp fluorescence histochemistry. *Brain Res. Bull.*. 9, 245-251.

[261]

[262] Leger, L., Charnay, Y., Hof, P.R., Bouras, C., Cespuglio, R. (2001) Anatomical distribution of serotonin-containing neurons and axons in the central nervous system of the cat. *J. Comp. Neural.,* 433, 157-182.

[263] Lester, R.A.J., Quarum, M.L., Parker, J.D., Wever, E., Jahr, C.E. (1989) Interaction of 6-cyano-7- nitroquinoxaline-2,3-dione with the N-methyl-D-aspartate receptor-associated glycine binding site. *Mol Pharmacol.,* 35, 565-570.

[264] Leung, C.G., Mason, P. (1999) Physiological properties of raphe magnus neurons during sleep and waking. *J. Neurophysiol.,* 81, 584-595.

[265] Levine, M.S., Cepeda, C. (1998) Dopaminergic modulation of responses mediated by excitatory amino acids in the neostriatum. *Adv. Pharmacol.,* 42, 724-729.

[266] Levy, R.A., Proudfit, H.K. (1979) Analgesia produced by microinjection of baclofen and morphine at brain stem sites. *Eur. J. Pharmacol.,* 57, 43-55.

[267] Li, A.H., Hwang, H.M., Tan, P.P., Wu, T., Wang, H.L. (2001) Neurotensin excites periaqueductal gray neurons projecting to the rostral ventromedial medulla. *J. Neurophysiol.,* 85, 1479-1488. Li, H.S., Monhemius, R., Simpson, B.A., Roberts, M.H.T. (1998) Supraspinal inhibition of nociceptive dorsal horn neurones in the anaesthetized rat: tonic or dynamic? *J. Physioi. (London),* 506, 459-469.

[268]

[269] Li, Y.Q., Takada, M., Kaneko, T., Mizuno, N. (1997) Distribution of GABAergic and glycinergic premotor neurons projecting to the facial and hypoglossal nuclei in the rat. *J. Comp. Neural,* 378, 283-294.

[270] Liebeskind, J.C., Guilbaud, G., Besson, J.M., Oliveras, J.L. (1973) Analgesia from electrical stimulation of the periaqueductal gray matter in the cat: behavioral observations and inhibitory effects on spinal cord interneurons. *Brain Res.,* 50, 441-446. Limberger, N.,

[271] Spath, L., Starke, K. (1991) Subclassification of the presynaptic (X2-autoreceptors in rabbit brain cortex. *Br. J. Pharmacol,* 103, 1251-1255.

[272] Lin, L., Faraco, J., Li, R., Kadotani, H., Rogers, W., Lin, X., Qie, X., de Jong, P.J., Nishino, S., Mignot, E. (1999) The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. *Cell,* 98, 365-376.

[273] Lindstrom, J., Schoepfer, R., Whiting, P. (1987) Molecular studies of the neuronal nicotinic acetylcholine receptor family. *Mol Neurobiol,* 1,281-337.

[274] Liinas, T. (1964) Mechanisms of supraspinal actions upon spinal cord activities. Pharmacological studies on reticular inhibition of alpha extensor motoneurons. J. *Neurophysiol,* 27, 1127-1137. Lord,

[275] J.A.H., Waterfield, A.A., Hughes, J., Kosterlitz, H.W. (1977) Endogenous opioid peptides: multiple agonists and receptors. *Nature,* 267, 495-499.

[276] Loring, R.H., Zigmond, R.E. (1988) Characterization of neuronal nicotinic receptors by snake venom neurotoxins. *TINS,* 11, 73-78.

[277] Luini, A., Goldberg, O., Teichberg, V.I. (1981) Distinct pharmacological properties of excitatory amino acid receptors in the rat striatum: a study by a Na^+ efflux assay. *Proc. Natl Acad. Sci. USA,* 78, 3250-3254.

[278] Lundberg, A., Vyklicky, L. (1966) Inhibition of transmission to primary afferents by electrical stimulation of the brain stem. *Arch. Hal Bio/.,* 104, 86-97.

[279] Luppi, P.H., Sakai, K., Fort, P., Salvert, D., Jouvet, M. (1988) The nuclei of origin of monoaminergic, peptidergic, and cholinergic afferents to the cat nucleus reticularis magnocellularis: a double-labeling study with cholera toxin as a retrograde tracer. *J. Comp. Neural,* 334, 466-476.

[280] Lynn, A.B., Herkenham, M. (1994) Localization of cannabinoid receptors and nonsaturable high-density cannabinoid binding sites in peripheral tissues of the rat - implications for receptor-mediated immune modulation by cannabinoids. *J. Pharmacol. Exp. Ther.,* 268, 1612-1623.

[281] MacDermott, A.B., Mayer, M.L., Westbrook, G.L., Smith, S.J., Barker, J.L. (1986) NMDA receptor activation increases cytoplasmic calcium concentration in cultured spinal cord neurons. *Nature,* 321,519-522.

[282] Maeno, H., Kiyama, R, Tohyama, M. (1993) Distribution of the substance P receptor (NK-1 receptor) in the central nervous system. *Mo!. Brain Res.,* 18, 43-58.

[283] Magoun, H.W. (1946) Caudal and cephalic influences of the brain stem reticular formation. *Physiol. Rev.,* 30, 459-474.

[284] Magoun, H.W., Rhines, R. (1946) An inhibitory mechanism in the bulbar reticular formation. *J. Neurophysiol,* 9, 165-171.

[285] Manaker, S., Tischler, L.J., Morrison, A.R. (1992) Raphespinal and reticulospinal axon collaterals to the hypoglossal nucleus in the rat. *J. Comp. Neurol.,* 322, 68-78.

[286] Mansour, A., Fox, C.A., Akil, H., Watson, S.J. (1995) Opioid-receptor mRNA expression in the rat CNS: anatomical and functional implications. *TINS,* 18, 22-29.

[287] Mantyh, P.W., Hunt, S.P. (1984) Evidence for cholecystokinin-like immunoreactive neurons in the rat medulla oblongata which project in the spinal cord. *Brain Res.,* 291, 49-54.

[288] Margeta-Mitrovic, M., Mitrovic, I., Riley, R.C., Jan, L.Y., Basbaum, A.I. (1999) Immunohistochemical localization of $GABA_B$ receptors in the rat central nervous system. *J. Comp. Neurol.,* 405,299-321.

[289] Marinelli, S., Vaughan, C.W., Schnell, S.A., Wessendorf, M.W., Christie, M.J. (2002) Rostral ventromedial medulla neurons that project to the spinal cord express multiple opioid receptor phenotypes. *J. Neurosci.,* 22, 10847-10855.

[290] Marlinskii, V.V., Voitenko, L.P. (1991) Participation of the medial reticular formation of the medulla oblongata in the supraspinal control of locomotor and postural activities in the guinea pig. *Fiziol. Z. SSSRIM Sechenova,* 77, 33-40.

[291] Maroteaux, L., Campanelli, J.T., Scheller, R.H. (1988) Synuclein: a neuron-specific protein localized to the nucleus and presynaptic terminal. *J. Neurosci.,* 8, 2804-2815.

[292] Martin, G., Montagne-Clavel, J., Oliveras, J.L. (1992) Involvement of ventromedial medulla "multimodal, multireceptive" neurons in opiate spinal descending control system: a single-unit study of the effect of morphine in the awake, freely moving rat. *J. Neurosci.,* 12,1511-1522.

[293] Martin, G.F., Waltzer, R. (1984) A double labelling study of reticular collaterals to the spinal cord and cerebellum of the North American opossum. *Neurosci. Lett.,* 47, 185-191.

[294] Martin, G.F., Vertes, R.P., Waltzer, R. (1985) Spinal projections of the gigantocellular reticular formation in the rat. Evidence for projections from different areas to laminae I and II and lamina IX. *Exp. Brain Res.,* 58, 154-162.

[295] Martin, W.J., Tsou, K., Walker, J.M. (1998) Cannabinoid receptor-... ,. mediated inhibition of the rat tail-flick reflex after microinjection into the rostral ventromedial medulla. *Neurosci. Lett.,* 242, 33-36.

[296] Martin, W.R., Eades, C.G., Thompson, J.A., Huppler, R.E., Gilbert, P.E. (1976) The effects of morphine- and nalorphine-iike drugs in the nondependent and morphine-dependent chronic spinal dog. *J. Pharmacol. Exp. Ther.,* 197, 517-532.

[297] Matsuda, L.A., Lolait, S.J., Brownstein, M.J., Young, A.L., Bonner, T.L. (1993) Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature,* 346, 561-564.

[298] Matsuyama, K., Ohta, Y., Mori, S. (1988) Ascending and descending projections of the nucleus reticularis gigantocellularis in the cat demonstrated by the anterograde neural tracer, *Phaseolus vulgaris* leucoagglutinin (PHA-L). *Brain Res.,* 460, 124-141.

[299] Mayer, M.L., Westbrook, G.L. (1984) Mixed-agonist action of excitatory amino acids on mouse spinal cord neurones under voltage clamp. *J. Physiol. (London),* 354, 29-53.

[300] Mayer, M.L., Westbrook, G.L., Guthrie, P.B. (1984) Voltage-dependent block by Mg^{2+} of NMDA responses in spinal cord neurons. *Nature,* 309, 261-263.

[301] Mazella, J., Botto, J.M., Guillemare, E., Coppola, T., Sarret, P., Vincent, J.P. (1996) Structure, functional expression, and cerebral

localization of the levocabastine-sensitive neurotensin/neuromedin N receptor from mouse brain. *J. Neurosci.,* 16, 5613-5620. McCann, D.J., Su, T.P.(1992) Stimulation of <t> ligand binding by phenytoin: apparent binding site and ligand specificity, in; Kamenka, J.M., Domino, E.F. Eds, Multiple sigma and PCP receptor ligands: mechanisms for neuromodulation ani neuroprotection? Ann Arbor, Michigan, NPP Books, pp. 295-305. McCreery, D.B., Bloedel, J.R., Hames, E.G. (1979) Effects of stimulating in raphe nuclei and in reticular formation on response of spinothalamic neurons to mechanical stimuli. *J. Neurophysiol,* 42, 166-182.
McGowan, M.K., Hammond, D.L. (1993) Intrathecal GABA, antagonists attenuate the antinociception produced by microinjection of „-glutamate into the ventromedial medulla of the rat. *Brain Res.,* 607, 39-46.
McGowan, M.K.., Hammond, D.L. (1993) Antinociceptio produced by microinjection of L-glutamate into the ventromedia medulla of the rat: mediation by spinal $GABA_A$ receptors. *Bra Res.,* 620, 86-96. McKinney, M., Anderson, D., Vella-Rountree, L. (1989) Different agonist-receptor active conformations for rat brain Ml and M2 muscarinic receptors that are separately coupled to two biochemical effector systems. *Mol Pharmacol.,* 35, 39-47. McLennan, H., Lodge, D. (1979) The antagonism of amino acid-induced excitation of spinal neurones in the cat. *Brain Res.,* 169, 83-90.
Mehler, W.R., Feferman, M.E., Nauta, W.H.I. (1960) Ascending axon degeneration following anterolateral chordotomy. An experimental study in the monkey. *Brain,* 83, 718-750. Meier, J., Schmieden, V. (2003) Inhibition of a-subunit glycine receptors by quinoxaline. *NeuroReport,* 14, 1507-1510. Meltzer, H.Y. (1994) An overview of the mechanism of action of clozapine. *J. Clin. Psychiat.,* 55, 47-52.
Menetrey, D., Basbaum, A.I. (1987) The distribution of substance P-, enkephalin- and dynorphin-immunoreactive neurons in the medulla of the rat and their contribution to bulbospinal pathways. *Neurosci.,* 23, 173-187.
Meng, X.W., Skinner, B.K.., Ohara, P.T., Fields, H.L. (1997) Noradrenergic input to nociceptive modulatory neurons in the rat rostral ventromedial medulla. *J. Comp. Neurol.,* 377, 381-391. Mierau, J., Schneider, F.J., Ensinger, H.A., Chio, C.L., Lajiness, M.E., Huff, R.M. (1995) Pramipexole binding and activation of cloned and expressed dopamine D2, D3 and D4 receptors. *Eur. J. Pharmacol.,* 290, 29-36.
Mileykovskiy, R.Y., kiyashchenko, L.I., Siegel, J.M. (2002) Muscle tone facilitation and inhibition after orexin-A (hypocretin-1) microinjections into the medial medulla. *J. Neurophysiol.,* 87, 2480-2489'
Millhorn, D.E., Seroogy, K., Hokfelt, T., Schmued, L.C., Terenius, L., Buchan, A., Brown, J.C. (1987) Neurons of the ventral medulla oblongata that contain both somatostatin and enkephalin immunoreactivities project to nucleus tractus solitarii and spinal cord. *Brain Res.,* 424, 99-108.
Minson, J., Pilowsky, P., Llewellyn-Smith, L, Kaneko, T., Kapoor, V., Chalmers, J. (1991) Glutamate in spinally projecting neurons of I the rostral ventral medulla. *Brain Res.,* 555, 326-331. Mitani, A., Ito, K., Hallanger, A.E., Wainer, B.H., Kataoka, K., I McCarly, R.W. (1988) Cholinergic projections from the laterodorsal and Pedunculopontine tegmental nuclei to the gigantocellular tegmental field in the rat. *Brain Res.,* 451, 397-402. Miura, M., Okada, J., Takayama, K. (1996) Parapyramidal rostro-ventromedial medulla as a respiratory rhythm modulator. *Neurosci. Lett.,* 203,41-44.
Mizuno, N., Yasui, Y., Nomura, S., Itoh, K.., Takada, M., Kudo, M. (1983) A light and electron microscopic study of premotor neurons for the trigeminal motor nucleus. *J. Comp. Neurol,* 215, 290-298. Mochizuki-Oda, N., Nakajima, Y., Nakanishi, S., Ito, S. (1994) Characterization of the substance P receptor-mediated calcium influx in cDNA transfected Chinese hamster ovary cells. A possible role of inositol 1,4,5-triphosphate in calcium influx. *J. Biol. Chem.,* 269,9651-9658.
Mohrland, J.S., Gebhart, G.F. (1980) Effects of focal electrical stimulation and morphine microinjection in the periaqueductal gray of the rat mesencephalon on neuronal activity in the medullary reticular formation. *Brain Res.,* 201, 23-37.

[322] Momiyama, T., Sim, J.A. (1996) Modulation ofinhibitory transmission by dopamine in rat basal forebrain nuclei: activation of presynaptic D|-like dopaminergic receptors. *J. Neuronsci.,* 16, 7505-7512.

[323] Monyer, H., Sprengel, R, Schoepfer, R., Herb, A., Higuchi, M., Lomeli, H., Burnashev, N., Sakmann, B., Seeburg, P.M. (1992) Heteromeric NMDA receptors: molecular and functional distinction of subtypes. *Science,* 256, 1217-1221.

[324] Morales, M., Battenberg, E., Bloom, F.E. (1998) Distribution of neurons expressing immunoreactivity for the 5HTj receptor subtype in the rat brain and spinal cord. *J. Conip. Neural.,* 385, 385-401.

[325] Moreau, J.L., Fields, H.L. (1986) Evidence for GABA involvement in midbrain control of medullary neurons that modulate nociceptivc transmission. *Brain Res.,* 397, 37-46.

[326] Morgan, M.M., Whitney, P.K. (2000) Immobility accompanies the antinociception mediated by the rostral ventromedial medulla of the rat. *Brain Res.,* 872, 276-281.

[327] Moriwaki, A., Wang, J.B., Svingos, A., van Bockstaele, E., Cheng. P., Pickel, V., Uhl, G.R. (1996) u. opiate receptor immunorcaclivity in rat central nervous system. *Neurochem. Res.,* 21, 1315-1331.

[328] Morrow, A.L., Creese, I (1986) Characterization of a,-adrenergic receptor subtypes in rat brain: a re-evaluation of [^{3}H]WB4101 and [^{3}H]prazosin binding. *Mole. PharmacoL,* 29, 285-287.

[329] Moruzzi, G., Magoun, H.W. (1949) Brain stem reticular formation and activation of the EEC. *EEC Clin. Neurophysiol..* 1, 445-473.

[330] Munro, S., Thomas, K..L., Abu-Shaar, M. (1993) Molecular characterization of a peripheral receptor for cannabinoids. *Nature,* 365,61-65.

[331] Murphy, D.D., Rueter, S.M., Trojanowski, J.Q., Lee, V.M.Y. (2000) Synucleins are developmentally expressed, and a-synuclein regulates the size of the presynaptic vesicular pool in primary hippocampal neurons. *J. Neurosci.,* 20, 3214-3220.

[332] Muscatt, S., Rothwell, J., Obeso, J., Leigh, N., Jenner, P., Marsden, C.D. (1986) Urea-induced stimulus-sensitive myoclonus in the rat. *Adv. Neural,* 43, 553-563.

[333] Nagata, T., Suzuki, H., Zhang, R., Ozaki, M., Kawakami, Y. (2003) Mechanical stimulation activates small fiber mediated nociceptive responses in the nucleus gigantocellularis. *Exp. Brain Res.,* 149, 505-511.

[334] Nakajima, Y., Iwakabe, H., Akazawa, C., Nawa, H., Shigemoto, R., Mizuno, N., Nakanishi, S. (1993) Molecular characterization of a novel retinal metabotropic glutamate receptor mGluR6 with a high agonist selectivity to $_L$-2-amino-4-phosphonobutyIate. *J. Bio/. Chem.,* 268, 11868-11873.

[335] Nakano, I., Hashizume, Y., Tomonaga, M. (1990) Bunina bodies in neurons of the medullary reticular formation in a case of amyotrophic lateral sclerosis. *Ada Neumpathol, 79,* 689-691.

[336] Nakano, I., Iwatsubo, T., Hashizume, Y., Mizutani, T. (1993) Bunina bodies in neurons of the medullary reticular formation in amyotrophic lateral sclerosis. *Ada Neuropathol,* 85, 471-474.

[337] Nakaya, Y., Kaneko, T., Shigemoto, R., Nakanishi, S., Mizuno, N. (1994) Immunohistochemical localization of substance P receptor in the central nervous system of the adult rat. *J. Camp. Neural.,* 347, 249-274.

[338] Nauta, W.J.H., Kuypers, G.J.M. (1958) Some ascending pathways in the brain stem reticular formation. In: Jasper, H.H., Proctor, L.D., Knighton, R.S., Nohay, W.C., Costillo, R.T. Eds, The reticular formation of the brain. Boston, Little Brown, pp. 3-30.

[339] Newman, D.B., Liu, R.P. (1987) Nuclear origins of brainstem reticulocortical systems in the rat. *Am. J. Anal.,* 178, 279-299.

[340] Newman, D.B., Hilleary, S.K., Ginsberg, C.Y. (1989) Nuclear terminations of corticoreticular fiber systems in rats. *Brain Behav. Evol.,* 34, 223-264.

[341] Newman, D.B., Ginsberg, C.Y. (1994) Brainstem reticular nuclei that project to the thalamus in rats: a retrograde tracer study. *Brain Behav. Evol.,* 44, 1-39.

[342] Ng, N.K., Lee, U.S., Wong, P.T. (1999) Regulation of striatal dopamine release through 5-HT1 and 5-HT2 receptors. *J. Neurosci. Res.,* 55, 600-607.

[343] Ngai, S.H., Wang, S.C. (1957) Organization of central respiratory mechanisms in the brain stem of the cat: localization by stimulation and destruction. *Am. J. Physiol,* 190, 343-349.

Nicola, S.M., Malenka, R.C. (1997) Dopamine depresses excitatory and inhibitory synaptic transmission by distinct mechanisms in the nucleus accumbens. *J. Neurosci.,* 17, 5697-5710.
Niimi, K., Kusunose, M., Ono, K., Yanagihara, M. (1990) Brainstem afferents to the intralaminar nuclei of the cat thalamus studied by the horseradish peroxidase method. *J. Hirnforsch.*. 31. 107-122.
Noga. B.R., Kettler, J., Jordan, L.M. (1988) Locomotion produced in mesencephalic cats by injections of putative transmitter substances and antagonists into the medial reticular formation and the pontomedullary locomotor strip. *J. Neurosci.,* 8, 2074-2086.
Noga, B.R., Kriellaars, D.J., Jordan, L.M. (1991) The effect of selective brainstem or spinal cord lesions on treadmill locomotion evoked by stimulation of the mesencephalic or pontomedullary locomotor regions. J. *Neurosci.*. 11, 1691-1700.
Nowak, L., Bregestovski, P., Ascher, P., Herbet, A., Prochiantz, A. (1984) Magnesium gates glutamate-activated channels in mouse central neurons. *Nature,* 307, 452-455.
Nybcrg-Hansen, R. (1965) Sites and mode of termination of rctictilo-spinal fibers in the cat. An Experimental study with silver impregnation methods. *J. Camp. Neural,* 124, 71-100.
O'Connor, L.H., Nock, B., McEwen, B.J. (1988) Regional specificity of gamma-aminobutyric acid receptor regulation by estradiol. *Neuroendocrinol,* 47, 473-481.
Odeh, P., Antal, M., Zagon, A. (2003) Hetrogeneous synnplic inputs from the ventrolateral periaqueductal gray matter to neurons responding to somatosensory stimuli in the rostromedial medulla of rats. *Brain Res.,* 959, 287-294.
Ohama, E., Ikuta. F. (1976) Parkinson's disease: distribution of Lewy bodies and monoamine neuron system. *Ada Neiiropulhol.,* 34,311-319.
Ohtake, T. (1992) Ascending projections from the gigantocellular reticular and dorsal paragigantocellular nuclei of the medulla oblongata in the rat: an anterograde PHA-L tracing study. *Neurosci. Res.,* 14,96-116.
Okamoto, K., Hirai, S., Shoji, M., Harigaya, Y., Fiikuda, T. (1991) Widely distributed Bunina bodies and spheroids in a case of atypical sporadic amyotrophic lateral sclerosis. *Ada Neuropalhol.*. 81,349-353.
Okuma, T., Fujimori, M. (1963) Eleetrographic and evoked potential studies during sleep in the cat (the study on sleep I). *Folia Psychiat. Neural. Jap.,* 17, 25-50.
Oliveras, J.L., Vos, B., Martin, G., Montague, J. (1989) Electrophysiological properties of ventromedial medulla neurons in response to noxious and non-noxious stimuli in the awake, freely moving rat: a single-unit study. *Brain Res.,* 486, 1-14.
Oliveras, J.L., Montague, J., Vos, B. (1990) Single unit activity at ventromedial medulla level in the awake, freely moving rat: effects of noxious and light tactile stimuli onto convergent neurons. *Brain Res.,* 506, 19-30.
Olson, E.J., Boeve, B.F., Silber, M.H. (2000) Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. *Brain,* 123, 331-339.
Ortells, M.O., Lunt, G.G. (1995) Evolutionary history of the ligand-gated ion-channel superfamily of receptors. *TINS.* 18. 121-127.
Palkovits, M., Jacobowitz, D.M. (1979) Topographical atlas of catecholamine and acetylcholinesterase-containing neurons in the rat brain. II. Hindbrain (mesencephalon, rhombencephalon). ./. *Camp. Neural,* 157, 29-42.
Pan, Z.Z., Tershner, S.A., Fields, H.L. (1997) Cellular mechanism for anti-analgesic action of agonists of the K-opioid receptor. *Nature,* 389, 382-385.
Paxinos, G., Watson, C. (1986) The rat brain in stereotaxic coordinates. 2nd Edition. Academic Press, San Diego.
Perciavalle, V. (1987) Substantia nigra influences on the reticulospinal neurons: an electrophysiological study in cats and rats. *Neurosci.,* 23, 243-251.
Pereda, A.E., Morales, F.R., Chase, M.H. (1990) Medullary control of lumbar motoneurons during carbachol-induced motor inhibition. *Brain Res.,* 514, 175-179.
Perreault, M.C., Drew, T., Rossignol, S. (1993) Activity of medullary reticulospinal neurons during fictive locomotion. *J. Neurophysiol,* 69, 2232-2247.

[366] Peters, A., Palay, S.L., Webster, H.D. (1991) Synapse. In: The fine structure of the nervous system. New York, Oxford Press, pp. 138-211.

[367] Peters, J.A., Callachan, K.H., Lamberg. J.J., Turner. A.J. (1988) Modulation of the GABA-A receptor by depressant barbiturates and pregnane steroids. *Br. J. Pharmacol,* 94, 1257-1269.

[368] Peterson, B.W., Maunz, R.A., Pitts, N.G., Mackel, R.G. (1975) Pattern of projection and branching of reticulospinal neurons. *Exp. Brain Res.*. 23, 333-351.

[369] Petralia, R.S., Wenthold, R.J. (1992) Light and electron immunocytochemical localization of AMPA-selective glutamate receptors in the rat brain. *J. Comp. Neural.,* 318, 329-354. [370] Petralia, R.S., Yokotani, N., Wenthold, R.J. (1994) Light and electron microscope distribution of the NMDA receptor subunit NMDAR1 in the rat nervous system using a selective anti-peptide antibody. *J. Neurosci.,* 14, 667-696.

[371] Petrash, A.C., Bylund, D.B. (1986) Alpha-2 adrenergic receptor subtypes indicated by ^{3}H-yohimbine binding in human brain. *Life Set,* 38, 2129-2137.

[372] Peyron, C., Tighe, O.K., van Den Pol, A.N., De Lecea, L., Heller, H.C., Sutcliffe, J.G., Kilduff, T.S. (1998) Neurons containing hypocretin (orexin) project to multiple neuronal systems. *J. Neurosci.,* 18, 9996-10015.

[373] Phillips, S., Gelgor, L., Mitchell, D. (1992) Antinociceptive action of dopamine agonists in the nucleus raphe magnus of rats is mediated by D2 receptors. *Arch Int. Pharmacodyn.,* 319, 66-75. [374] Piercey, M.F., Hoffman, W.E., Smith, M.W., Hyslop, O.K. (1996) Inhibition of dopamine neuron firing by pramipexole, a dopamine D3 receptor-preferring agonist: comparison to other dopamine receptor agonists. *Eur. J. Pharmacol.,* 312, 35-44.

[375] Pin, J.P., Waeber, C., Prezeau, L., Bockaert, J., Heinemann, S.F. (1992) Alternative splicing generates metabotropic glutamate receptors inducing different patterns of calcium release in *Xenopus* oocytes. *Proc. Natl. Acad. Sci. USA,* 89, 10331-10335.

[376] Pitts, R.F., Magoun, H.W., Ranson, S.W. (1939) Localization of the medullary respiratory centers in the cat. *Am. J. Physio!.,* 190, 343-349.

[377] Pommier, B., Da Nascimento, S., Dumont, S., Bellier, B., Million, E., Garbay, C., Roques, B.P., Noble, F. (1999) The CCK.-B receptor is coupled to two effector pathways through pertussis sensitive and insensitive G proteins. 7. *Neurochem.,* 73, 281-288. [378] Pompeiano, O., Swett, J.E. (1963) Actions of graded cutaneous and muscular afferent volleys on brain stem units in the decerebrate, cerebellectomized cat. *Arch Ital. Biol.,* 101, 552-583. [379] Portillo, F., Grelot, L., Milano, S., Bianchi, A.L. (1994) Brainstem neurons with projecting axons to both phrenic and abdominal motor nuclei: a double fluorescent labeling study in the cat. *Neurosci. Lett.,* 173, 50-54. [380] Probst A., Cortes, R., Palacios, J.M. (1986) The distribution of [402] glycine receptors in the human brain. A light microscopic autoradiographic study using [^{3}H]strychnine. *Neurosci.,* 17, 11-35. [381] Quirion, R., Chicheportiche, P.C., Contrearas, K.M., Johnson, D., Lodge, S., Tarn, W., Woods, J.H., Zukin, S.R. (1987) Classification and nomenclature of phencyclidine and sigma receptor sites. *TINS,* 10, 444-446.

[382] Racca, C., Gardiol, A., Triller, A. (1998) Cell-specific dendritic localization of glycine receptor a subunit messenger RNAs. *Neurosci.,* 84, 997-1012.

[383] Radnikow, G., Misgeld, U. (1998) Dopamine D, receptors facilitate $GABA_A$ synaptic currents in the rat substantia nigra pars reticulata. *J. Neurosci.,* 18,2009-2016.

[384] Rainbow, T.C., Schwartz, R.D., Parsons, B., Kellar, K.J. (1984) Quantitative autoradiography of nicotinic [^{3}H]-acetylcholine binding sites in rat brain. *Neurosci. Lett.,* 50, 193-196.

[385] Rampon, C., Luppi, P.H., Fort, P., Peyron, C., Jouvet, M. (1996) Distribution of glycine-immunoreactive cell bodies and fibers in the rat brain. *Neurosci.,* 75, 737-755. [386] Rampon, C., Peyron, C., Petit, J.M., Fort, P., Gervasoni, D., Luppi, P.H. (1996) Origin of the glycinergic innervation of the rat trigeminal motor nucleus. *NeuroReport,* 7, 3081-3085.

[387] Randle, J.C.R., Guet, T., Bobichon, C., Moreau, C., Curutchet, P., lambolez, B., Prado de Carvalho, L., Cordi, A., Lepagnol, J.M. (1992) Quinoxaline derivatives: structure-activity relationships and physiological implications of inhibition of N-methyl-D-aspartate and non-N-methyl-D-aspartate receptor-mediated currents and synaptic potentials. *Mo/. Pharmacol.,* 41, 337-345.

[388] Reddy, V.K., Cassini, P., Ho, R.H., Martin, G.F. (1990) Origins and terminations of bulbospinal axons that contain serotonin and either enkephalin or substance-P in the North American opossum *J. Comp. Neural,* 294, 96-108.

[389] Regoli, D., Boudon, A., Fauchere, J.L. (1994) Receptors and antagonists for substance P and related peptides. *Pharmacol. Ret.* 46,551-599.

[390] Reichling, D.B., Basbaum, A.I. (1990) Contribution of brainstem GABAergic circuitry to descending antinociceptive controls: I. GABA-immunoreactive projection neurons in the periaqueductal gray and nucleus raphe magnus. *J. Comp. Neural.,* 302, 370-377.

[391] Reith, C.A., Sillar, K.T. (1997) Pre- and postsynaptic modulation of spinal GABAergic neurotransmission by the neurosteroid. 5f-pregnan-3a-ol-20-one. *Brain Res.,* 770, 202-212.

[392] Rho, M.J., Cabana, T., Drew, T. (1997) Organization of the projections from the pericruciate cortex to the pontomedullan reticular formation of the cat: a quantitative retrograde tracing study. *J. Comp. Neural.,* 388, 228-249.

[393] Richard, C.A., Waldrop, T.G., Bauer, R.M., Mitchell, J.H. Stremel, R.W. (1989) The nucleus reticularis gigantocellulatis modulates the cardiopulmonary responses to central and peripheral drives related to exercise. *Brain Res.,* 482, 49-56.

Richard, C.A., Stremel, R.W. (1990) Involvement of the raphe i: the respiratory effects of gigantocellular area activation. *Brain fa Bull,* 25, 19-23.

[394] Roger, S.D., Harris, D.C.H., Steward, J.H. (1991) Possible relatir between restless legs and anemia in renal dialysis patients. *LIIIK.'* 1, 1551.

[395] Romagnano, M.A., Harshbarger, R.J., Hamill, R.W. (1991)1 Brainstem enkephalinergic projections to spinal autonomic nuclei.! *J. Neurosci.,* 11,3539-3555.

[396] Ross, G.S., Sinnamon, H.M. (1984) Forelimb and hindlin stepping by the anesthetized rat elicited by electrical stimulation I the pons and medulla. *Physio/. Behav.,* 33, 201-208.

[397] Rossi, G.C., Pasternak, G.W., Bodnar, R.J. (1994) u and 6 opioiJl synergy between the periaqueductal gray and the rostro-ventral| medulla. *Brain Res.,* 665, 85-93.

[398] Rossi, G.F., Brodal, A. (1956) Corticofugal fibres to the brain-stall reticular formation. An experimental study in the cat. *J. Anal.,t* 42-63.

[399] Rossi, G.F., Brodal, A. (1957) Terminal distribution of| spinoreticular fibers in the cat. *Arch Neural. Psychial.,* 78,4 453.

[400] Roush, E.D., Kwatra, M.M. (1998) Human substance P recepl«| expressed in Chinese hamster ovary cells directly activates G(alpk q/11), G(alpha s), G(alpha o). *FEBSLett.,* 428, 291-294.

[401] Roychowdhury, S.M., Fields, H.L. (1996) Endogenous opio: acting at a medullary |i-opioid receptor contribute to the behi antinociception produced by GABA antagonism in the midl periaqueductal tray. *Neurosci.,* 74, 863-872.

Saade, N., Salibi, N.A., Banna, N.R., Towe, A.L., Jabbur.SJj (1983) Spinal input pathways affecting the medulla gigantocellular reticular nucleus. *Exp. Neural.,* 80, 582-600.

[403] Saano, V. (1987) GABA-benzodiazepine receptor complex i drug actions. *Med. Biol.,* 65, 167-176.

Sakai, K., Yoshimoto, Y., Luppi, P.H., Fort, P., El Mansari.1

[404] Salvert, D., Jouvet, M. (1990) Lower brainstem afferents to the (j posterior hypothalamus: a double-labeling study. *Brain Res. I*

[405] 24, 437-455.

Sakurai, T., Amemiya, A., Ishii, M., Matsuzaki, I., Chemelli.R Tanaka, H., Williams, S.C., Richardson, J.A., Kozlowski,(Wilson, S., Arch, J.R., Buckingham, R.E., Haynes, A.C., (

[406] S.A., Annan, R.S., McNulty, D.E., Liu, W.S., Terretl, JJ| Elshourbagy, N.A., Bergsma, D.J., Yanagisawa, M. (1998)C and orexin receptors: a family of hypothalamic neuropeptides* G protein-coupled receptors that regulate feeding behavior. *C* 92, 573-585.

Sandkuhler, J., Gebhart, G.F. (1984) Relative contributionsof| nucleus raphe magnus and adjacent medullary reticular fora to the inhibition by stimulation in the periaqueductal grayd

[407] spinal nociceptive reflex in the pentobarbital-anesthelized« *Brain Res.,* 305, 77-87.

[408] Sasa, M., Ishihara, K.., Amano, T., Matsubayashi, H., Momiyama, T., Todo, N. (1997) D_2 receptor activation in distinct striatal neurons in comparison with D_3 receptors. *Jpn. J. PsychopharmacoL,* 17,97-100.

[409] Sasek, C.A., Wessendorf, M.W., Helke, *C.I.* (1990) Evidence for co-existence of thyrotropin-releasing hormone, substance P and serotonin in ventral medullary neurons that project to the intermediolateral cell column in the rat. *Neurosci.,* 35, 105-119.

[410] Sato, K.., Kiyama, H., Tohyama, M. (1992) Regional distribution of cells expressing glycine receptor a_2 subunit mRNA in the rat brain. *Brain Res.,* 590,95-108.

[411] Sato, K.., Kiyama, H., Tohyama, M. (1993) The differential expression patterns of messenger RNAs encoding non-N-methyi-u-aspartate glutamate receptor subunits (GluRl-4) in the rat brain. *Neurosci.,* 52,515-539.

[412] Satoh, M., Akaike, A., Nakazawa, T., Takagi, H. (1980) Evidence for involvement of separate mechanisms in the production of analgesia by electrical stimulation of the nucleus reticularis paragigantocellularis and nucleus raphe magnus in the rat. *Brain* to., 194, 525-529.

[413] Satoh, M., Oku, R., Akaike, A. (1983) Analgesia produced by micromjection of L-glutamate into the rostral ventromedial bulbar nuclei of the rat and its inhibition by intrathecal a-adrenergic blocking agents. *Brain Res.,* 261, 361-364.

[414] Scheibel, M., Scheibel, A., Mollica, A., Moruzzi, G. (1955) Convergence and interaction of afferent impulses on single units of reticular formation. *J. Neurophysioi.,* 18,309-331.

[415] Schenck, C.H., Bundlie, S.R., Ettinger, M.G., Mahowald, M.W. (1986) Chronic behavioral disorders of human REM sleep: a new category of parasomnia. *Sleep,* 9, 293-308.

[416] Schenck, C.H., Bundlie, S.B., Mahowald, M.W. (1996) Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder. *Neurology,* 46, 388-393.

[417] Schenkel, E., Siege], J.M. (1989) REM sleep without atonia after lesions of the medial medulla. *Neurosci. Lett.,* 98, 159-165.

[418] Schenkel, E., Lai, Y.Y., Siegel, J.M. (1989) Loss of muscle tone after electrical or chemical stimulation of the medial medulla in the intact cat. *Soc. Neurosci. Abstr.,* 15, 391.

[419] Schwinn, D.A., Lomasney, J.W., Lorenz, W., Szklut, P.J., Fremeau, R.T. Jr., Yang-Feng, T.L., Caron, M.G., Lefkowitz, R.J., Cotecchia, S. (1990) Molecular cloning and expression of the cDNA for a novel cti-adrenergic receptor subtype. *J. Bio/. Chem.,* 265,8183-8189.

[420] Segundo, J.P., Takenaka, T., Encabo, H. (1967) Somatic sensory properties of bulbar reticular neurons. *J. Neurophysioi.,* 30, 1221-1238.

[421] Semba, K., Fibiger, H.C. (1992) Afferent connections of the laterodorsal and the Pedunculopontine tegmental nuclei in the rat: a retro- and antero-grade transport and immunohistocliemical study. *J. Comp. Neural.,* 323. 387-410.

[422] Shapiro, R.A., Scherer, N.M., Habecker, B.A., Subers, E.M., Nathanson, N.M. (1988) Isolation, sequence and functional expression of the mouse Ml muscarinic acetylcholine receptor gene./ *Bio/. Chem.,* 263, 18397-18403.

[423] Shefchyk, S.J., Jell, R.M., Jordan, L.M. (1984) Reversible cooling of the brainstem reveals areas required for mesencephalic locomotor region evoked treadmill locomotion. *Exp. Brain Res.,* 56,257-262.

[424] Shen, K.Z., Johnson, S.W. (2000) Presynaptic dopamine D_2 and muscarine *M,* receptors inhibit excitatory and inhibitory transmission to rat subthalamic neurones *in vitro. J. Physiol. (London),* 525, 331-341.

[425] Shen, M., Piser, T.M., Seybold, V.S., Thayer, S.A. (1996) Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. *J. Neurosci.,* 16, 4322-4334.

1426] Shen, P., Arnold, A.P., Micevych, P.E. (1990) Supraspinal projections to the ventromedial lumbar spinal cord in adult male rats../. *Comp. Neural..* 300, 263-272.

[427] Shiromani, P.J., Armstrong. D.M., Gillin, J.C. (1988) Cholinergic neurons from the dorsolateral pons project to the median pons: a WGA-HRP and ChAT immunohistochemieal study. *Neurosci. LeU., 95,* 19-23.

Shults, C.W., Quirion, R., Chronwall, B., Chase, T.N., O'Donohue, T.L. (1984) A comparison of the anatomical distribution of substance P and substance P receptors in the rat central nervous system. *Peptides,* 5, 1097-1128.
Sibley, D.R., Creese, I. (1983) Interactions of ergot alkaloids with anterior pituitary D-2 dopamine receptors. *Mole. Pharmacol.,* 23, 585-593.
Siegel, J.M. (1979) Behavioral functions of the reticular formation. *Brain Res. Rev.,* 1,69-105.
Siegel, J.M., Wheeler, R.L., McGinty, D..I. (1979) Activity of medullary reticular formation neurons in the unrestrained cat during waking and sleep. *Brain Res.,* 179, 49-60.
Siegel, J.M., Tomaszewski, K..S. (1983) Behavioral organization of reticular formation: studies in the unrestrained cat. I. Cells related to axial, limb, eye, and other movements. *J. Neurophysioi..* 50. 696-716.
Siegel, J.M., Tomaszewski, K.S., Wheeler, R.L. (1983) Behavioral organization of reticular formation: studies in the unrestrained cat. I. Cells related to facial movements. *J. Neurophysioi.,* 50, 717-723.
Siegel, J.M., Nienhuis, R., Fahringer, H.M., Paul, R., Shiromani, P., Dement, W.C., Mignot, E., Chiu, C. (1991) Neuronal activity in narcolepsy: identification of cataplexy-related cells in the medial medulla. *Science,* 252, 1315-1318.
Sigel, E., Baur, R. (1988) Allosteric modulation by benzodiazepine receptor ligands of the $GABA_A$ receptor channel expressed in *Xenopus* oocytes. *J. Neurosci.,* 8, 289-295.
Simerly, R.B., Swanson, L.W. (1988) Projections of the medial preoptic nucleus: a *Phaseolus vulgaris* leucoagglutinin anterograde tract-tracing study in the rat../. *Comp. Neural.,* 270, 209-242.
Simonneaux, V., Eabdi, M., Bylund, D.B. (1991) Identification and characterization of o^n-adrenergic receptors in bovine pineal gland. *Mole. Pharmacol.,* 40, 235-241.
Skagerberg, G., Bjorkiund, A. (1985) Topographic principles in the spinal projections of serotonergic and non-serotonergic brainstem neurons in the rat. *Neurosci.,* 15, 445-480.
Skinner, K., Basbaum, A.I., Fields, H.L. (1997) Cholecystokinin and enkephalin in brain stem pain modulating circuits. *NeuroReport,* 8, 2995-2998.
Snider, R.S., Niemer, W.T. (1961) A stereotaxic atlas of the cat brain. Chicago: Univ Chicago Press.
Soja, P.J., Morales, F.R., Baranyi, A., Chase, M.H. (1987) Effect of inhibitory amino acid antagonists on IPSPs induced in lumbar motoneurons upon stimulation of the nucleus reticularis gigantocellularis during active sleep. *Brain Res.,* 423, 353-358.
Sontheimer, H., Becker, C.M., Pritchett, D.B., Schofield, P.R., Grenningloh, G., Kettenmann, H., Seeburg, P.H. (1989) Functional chloride channels by mammalian cell expression of rat glycine receptor subunit. *Neuron,* 2, 1491-1497.
Spencer, D.G. Jr., Horvath, E., Traber, J. (1986) Direct autoradiographic determination of MI and M_2 muscarinic acetylcholine receptor distribution in the rat brain: relation to cholinergic nuclei and projections. *Brain Res.,* 380, 59-68.
Spencer, R.F., Wenthold, R.J., Baker, R. (1989) Evidence for glycine as an inhibitory neurotransmitter of vestibular. reticular, and prepositus hypoglossal neurons that project to the cat abducens nucleus. *J. Neurosci.,* 9, 2718-2736.
Spinella, M., Schaefer, L.A., Bodnar, R.J. (1997) Ventral medullary mediation of mesencephalic morphine analgesia by muscarinic and nicotinic cholinergic receptor antagonists in rats. *Analgesia,* 3, 119-130.
Spinella, M., Znamensky, V., Moroz, M., Ragnauth, A., Bodnar, R.J. (1999) Actions of NMDA and cholinergic receptor antagonists in the rostral ventromedial medulla upon p-endorphin analgesia elicited from the ventrolateral periaqueductal gray. *Brain Res..* 829, 151-159.
St. John, W.M., Wang, S.C. (1976) Integration of chemoreceptor stimuli by caudal pontile and rostral medullary sites. *J. Appl. Physiol.,* 41,612-622.
Stella, N., Schweitzer, P., Piomelli, D. (1997) A second endogenous cannabinoid that modulates long-term potentiation. *Nature,* 388, 773-778.
Stoof, J.C., Kebabian, J.W. (1984) Two dopamine receptors: biochemistry, physiology and pharmacology. *Life Sci.,* 35, 2281-2296.

[450] Slomeita, R.I,., Guycnet, P.O. (1999) Distribution of glutamic acid decarbo\ylase mRNA-containing neurons in rat medulla projecting to thoracic spinal cord in relation to monoamincrgic brainstem neurons. *J. Comp. Neurol.,* 407, 367-380.

[451] Stremel, R.W., Waldrop, T.G., Richard, C.A., Iwamofo, G.A. (1990) Cardiorespiratory responses to stimulation of the nucleus reticularis giganlocellularis. *Brain Res. Hull.,* 24, 1-6.

[452] Su, C.K.. Yen, C.T., Chai, C.Y., Kuo, J.S. (1991) Neurons in the medullary gigantoceliular reticular nucleus mediate cardioinhibition in cats. *Chinese J. Physio/.,* 34, 399-412.

[453] Tabcr. E. (1961) The cytoarchilecture ofllie brain slum of the eat. I. Brain stem nuclei of cat. *J. Comp. Neuro/..* 116, 27-70.

[454] Tachibana, M, Tanaka, K., Hishikawa, Y., Kancko, 2. (1975) A sleep study of acute psychotic states due to alcohol and .**'. mcprobamate addiction. In: Wcitxman, li.D. Ed, Advances in sleep research. New York: Spectrum, pp, 177-203.

[455] Takiula, M., [loh, K.., Yasui, Y., Milani, A.. Nomura, S., Mi/.uno, N. (1984) Distribution of premotor neurons for (he hypoglossal nucleus in the cat. *Neurosci. Lett.,* 52, 141-146. [456] Takahashi, '!".. Berger. A.J. (1990) Direct excitation of rat spinal motoneurones by serotonin. *J. Physio!. (London),* 423, 63-76.

J457J Takakusaki, κ'. Ohta, Y., Mori, S. (1989) Single medullary reficulospinal neurons exert postsynaptic inhibitory effects via inhibitory internenrons upon alpha-motoneurons innervating cal hindlimb muscles. *Exp. Brain Res.,* 74, 11-23. [458] Tanabe, Y., Masu. M., Ishii. T.. Shigemoto, R,, Nakanishi, S. (1992) A family of malabotropic glutamalc receptors. *Neuron.* 8, 169-179. '"

[459] Tanabe, Y., Nomura. A.. Masu, M., Shigemoto, R., Mizuno, N.. Nakanishi, S. (1993) Signal transduction. pharmacological properties, and expression patterns of two metabotropic glutamalc receptors, mGluR3 and mGluR4../ *Neurosci.,* 13, 1372-1376. [460] Tanaka, K., Masu, M., Nakanishi, S. (1990) Structure and functional expression of the cloned rat neurotensin receptor. *Neuron,* 4, 847-854. [461] Tanaka, M., Okamura, H., Yanaihara, N., Tanaka, Y., Ibata, Y. (1993) Differential expression of serotonin and [Met]enkcphalin-Arg^{6}-Gly^{7}-Leu^{N} in neurons of the rat brain stem. *Brain Rex. Bull.,* 30,561-570. [462] Tanaka, M.. Okamura, 11.. Tamada. Y., Nagatsu, I., Tanaka, Y., Ibata, Y. (1994) Catecholamincrjiic input to spinally projecting serotonin neurons in ihc rostral ventromcdial medulla oblongala of the rat. *Brain Res. Bull.,* 35. 23-30. [463] Tattcrsall, .I.E., Cervero, F., Lumb, B.M. (1986) Viscerosomatie neurons in the lower thoracic spinal cord of the cat: excitations and inhibitions evoked by splanchnic and somatic nerve volleys and by stimulation of brain stem nuclei. *J. NeurophysioL,* 56, 1411-1423.

[464] Tayior, B.K., Basbaum, A.I. (1995) Neurochemical characterization of extracellular serotonin in the rostromedial medulla and its modulation by noxious stimuli. *J. Neurochem..* 65. 578-589. [465] Tebecis. A.K., DiMaria, A. (1972) Strychnine-sensitive inhibition in the medullary reticular formation: evidence for glycine as an inhibitory transmitter. *Brain Res.,* 40, 373-383.

14661 Tliannickal, T.C., Moore, R.Y., Nicnhuis, R., Ramanathan, L., Gulyani, S., Aldrich, M., Comford, M., Siegel, J.M. (2000) Reduced number of hypocretin neurons in human narcolepsy. *Neuron,* 27, 469-474. [467] Thomas, D.A., McGowan, M K., Hammond, D.L. (1995) Microinjection of baclofen in the ventromedial medulla of the rat produces antinociception or hyperalgesia. *J. Pharmacol. Kxp. Ther.,* 275. 274-284. [468J Tlior, K.B., Blilz-Sicbcrt, A., Helke, C..I. (1992) Autoradiographic localization of 5HT$_{1}$ binding sites in the medulla oblongata of the rat. *Synapse.* 10, 185-205.

[469] Thorat, S.N., Hammond, D.I,. (1997) Modulation of noeiception by micro inject ion of delta-1 and delta-2 opioid receptor ligands in the ventromcdial medulla of the rat. *J. Pharmacol. fcxp. Ther.,* 283, 1185-1192.

[470] Tliurston. C.L., Randich, A. (1995) Responses of on and off cells in the rostral ventral medulla to stimulation of vagal afferents and changes in mean arterial blood pressure in intact and eardiopulmonary deafferented rats. *Pain,* <i2, 19-38.

[471] Thurston-Stanfield, C.L., Ranicri. J.T., Vakkabhapurapu, R., Barnes-Noblc, D. (1999) Role of vagal afferents and the rostral

ventral medulla in intravenous serotonin-induefd changes in nocieeption and arterial blood pressure *Physio/, ftshcn.*. 67,753-767.
Ticku, M.K., Rastogi, S.K. (1986) Barbiturate-sensitive silts inlhc benzodiazepine-GABA rceptor-ionophore complex. In: Rotli, S.M., Miller, K.W. Hds. Molecular and cellular mechanisms of anesthetics. New York, Plenum, pp. 179-188.
Tolle, A., Fcldman. S.. Clementc, C.D. (1959) Effects of bulbar stimulation and dccerebration on visceral afferent responses in the spinal cord. *Am. J. Physio/.,* 196, 674-680.
Travers, J.B., Norgren, R. (1983) Afferent projections to the oral motor nuclei- *J. Comp. NeuroL.* 220. 280-298.
Tseng, L.L.F., Tang. R.. Stackman, R., Camara, A.. Fujiniolo. J.M. (1990) Brainstem sites differentially sensitive to p-endorphin a morphine for analgesia and release of Met-enkephalin anesthetized rats. J. *Pharmacol. Exp. Ther.,* 253, 930-937.
Tsunoda. Y., Owyang, C. (1993) Differential involvement of phospholipase A2αrachidonic acid and phospholipasc C/phosphoinositol pathways during cholecystokinin oscillations in pancreatic acini. *Biochm. Biophys Res. Conumtn.,* 194.1194-1202.
Tyler, M.R. (1968) Neurological disorders in renal failure. *Am. J. Mad,* 44, 734-748.
Uchiyama, M.. Isse, K., Tanaka, K.., Yokota, N., Hamamotn, M. Aida, S., Uo, Y., Yoshimura, M., Okawa, M. (1995) Incidcnla Lewy body disease in a patient with REM sleep behavior disorder. *Neurology,* 45, 709-7i2.
Urban. M.O., Smith, DJ. (1994) Localixation of Ihe antinociceptive and antianalgcsic effects of neurotensin wilhin the rostral venlromedial medulla. *Neurosci. Lett.,* 174, 21-25.
Urban, MO., Smith, D.J. (1994) Nuclei within the rostral ventromedia! medulla mediating morphine antinociception from the periaqucductal gray. *Brain Res.*. 652, 9-16.
Urban, M.O., Coulinho, S.V., Gebharl, G.E. (1999) Biphasic I modulation of viscera! nocieeption by neurotensin in rat rostral ventromedial medulla. *J. Pharmacol. Exp. Ther.*. 290, 207-213.
Van Bockslaele, E.J.. Aston-Jones, G., Pieribone, V.A., Ennis. M., Shiple, M.T. (1991) Subregions of the periaqueducta! gray topographically innervate the rostral ventral medulla in the ral. *J. Comp. NeuroL.* 309, 305-327.
Van Den Pol, A.N., Gao, X.B., Obrictan, K., Kilduff, T S., Belousov, A.B. (1998) Presynaplic and postsynaptic actions and modulation of neuroendocrine neurons by a new hypothalaniic peptide, hypocrctin/orexin. *J. Neurosci.,* 18, 7962-7971.
VanderMaelen, C.P., Aghajanian, O.K. (1980) Intracellular studies showing modulation of facial motoneurone excitability by serotonin. *Nature,* 287. 346-347.
Vanegas, H., Barbara, N.M., Fields, H.L. (1984) Tail-flick related activity in mcdullospinal neurons. *Brain Rex.,* 321, 135-141.
Van Tol, H.H.M., Bunzow, J.R., Guan, H.C., Simahara, R.K.. Seeman, P., Niznik, KB., Civelli, O. (1991) Cloning of the gene for a human dopamine Dj receptor with high affinity for the antipsychoticclozapine. *Nature,* 350, 610-614.
Varner, K.J., Rutherford, D.S., Vasquez, B.C., Brody, M.J. (1992) Identification of cardiovascular neurons in the rostral ventromedial medulla in anesthetized rats. *Hypertension,* 19, Suppl II, 193-197.
Vaughan, C.W., McGregor, I.S., Christie, M.J. (1999) Cannabinoid receptor activation inhibits GABAergic neurotransmission in rostral ventromedial medulla neurons *in vitro. Br. J. Pharmacol.*. 127,935-940.
Vertes, R.P. (1979) Brain stem gigantoceliular neurons: Patterns of activity during behavior and sleep in the freely moving rat. *J NeurophysioL,* 42,214-228.
Vertes, R.P. (1988) Brainstem afferents to the basal forebrain in the rat. *Neurosci., 24,* 907-935.
Vertes, R.P., Martin, G.F., Wallzer, R. (1986) An auloradiographic analysis of ascending projections from the medullary reticular formation in the rat, *Neruosci.,* 19, 873-898.
Vertes. R.P., Kocsis, B. (1994) Projections of the dorsal raplie nucleus to the brainstem: PIJA-L analysis in the rat. *J. Comp. NeuroL,* 340, 11-26.
Vertes, R.P., Crane, A.M. (1996) Descending projections of the posterior nucleus of" the hypothalamus: *Phaseoμs vulgar is* leneoagglutinin analysis in the rat. *J. Comp. Neuro/.,* 374,

[494] Vita, N., Laurent, P., Lefort, S., Chalon, P., Dumont, X., Kaghad, M., Gully, D., Le Fur, G., Fcrrara, P., Caput, D. (1993) Cloning and expression of a complementary DNA encoding a high affinity human neurotensin receptor. *FEBS Lett.,* 317, 139-142.

[495] Wada, K., Ballivet, M., Boulter, J., Connoll, J., Wada, E., Deneris, E.S., Swanson, L.W., Heinemann, S., Patrick, J. (1988) Functional expression of a new pharmacological subtype of brain nicotinic acetylcholine receptor. *Science,* 240, 330-334.

[496] Waltzer, R., Martin, G.F. (1988) Organization of forebrain projections from the medullary reticular formation in the North American opossum. Evidence for connectional heterogeneity. *Brain Behav. Evol.,* 31, 57-81.

[497] Wang, H., Wcssendorf, M.W. (1999) μ- and δ-opioid receptor mRNAs are expressed in spinally projecting serotonergic and nonserotonergic neurons of the rostral ventromedial medulla. *J. Comp. Neurol.,* 404, 183-196.

[498] Watanabe, M., Mishina, M., Inoue, Y. (1994) Distinct distribution of five NMDA receptor channel subunit mRNAs in the brainstem. *J. Comp. Neurol,* 343, 520-531.

[499] Watkins, J.C., Evans, R.H. (1981) Excitatory amino acid transmitters. *Ann. Rev. Pharmacol. Toxicol,* 21, 165-204. [500] Weiss, S., Sebben, M., Garcia-Saomz, J.A., Bockaert, J. (1985) D2-dopamine receptor-mediated inhibition of cyclic AMP formation in striatal neurons in primary culture. *Mol. Pharmacol,* 27, 595-599.

[501] Wetter, T.C.. Stiasny, K., Kohnen, R., Oertel, W.H., Trenkwalder, C. (1998) Polysomnographic sleep measures in patients with uremic and idiopathic restless legs syndrome. *Move. Disorders,* 13, 820-824.

[502] Wetter, T.C., Collado-Seidel, V., Pollmacher, T., Yassouridis, A., Trenkwalder, C. (2000) Sleep and periodic leg movement patters in drug-free patients with Parkinson's disease and multiple system atrophy. *Sleep,* 23, 361-367.

Whiting, P., Lindstrom, J. (1987) Purification and characterization of a nicotinic acetylcholine receptor from rat brain. *Proc. Natl. Acad. Sci. USA,* 84,595-599.

Winkelman, J.W., Chertow, G.M., Lazaurs, J.M. (1996) Restless legs syndrome in end stage renal disease. *Am. J. Kidney Dis.,* 28, 372-378.

Wishart, G., Bremner, D.H., Sturrock, K.R. (1999) Molecular modelling of the 5-hydroxytryptamine receptors. *Receptors & Channels,* 6,317-335.

[506] Wolstencroft, J.H. (1964) Reticulospinal neurones. *J. Physiol. (London),* 174, 91-108.

[507] Wu, K.M., Martin, W.R., Kamerling, S.G., Wettstein, J.G. (1983) Possible meudllary K hyperalgesic mechanism. I. A new potential role for endogenous opioid peptides in pain perception. *Life Sci.,* 33,1831-1838.

[508] Yang, K., Ma, W.L., Feng, Y.P., Dong, Y.X., Li, Y.Q. (2002) Origins of $GABA_B$ receptor-like immunoreactive terminals in the rat spinal dorsal horn. *Brain Res. Bull,* 58, 499-507.

[509] Yen, C.T., Blum, P.S. (1984) Response properties and functional organization of neurons in midline region of medullary reticular formation. *J. Neurophysiol,* 52, 961-979.

[510] Yen, C.T., Hwang, J.C., Su, C.K., Lin, Y.F., Yang, J.M., Chai, C.Y. (1991) Differential actions of the medial region of caudal medulla on autonomic nerve activities. *Clin. Exp. Pharmacol. Physiol,* 18,743-751.

[511] Yoshio, R., Taniguchi, T., Itoh, H., Muramatsu, I. (2001) Affinity of serotonin receptor antagonists and agonists to recombinant and native α_1-radrenoreceptor subtypes. *Jpn. J. Pharmacol.,* 86, 189-195.

[512] Young, A.B., Chu, D. (1990) Distribution of GABA-A and GABA-B receptors in mammalian brain: potential targets for drug development. *Drug Dev. Res.,* 21, 161-167.

Young, C.A., MacKenzie, J.M., Chadwick, D.W., Williams, I.R. (1993) Opsoclonus-myoclonus syndrome: an autopsy study of three cases. *Eur. J. Med.,* 2, 239-241.

[513] Young, W.S. III, Kuhar, M.J. (1981) Neurotensin receptor localization by light microscopic autoradiography in rat brain. *Brain Res.,* 206, 273-285.

[514] Zagon, A., Bacon, S.J. (1991) Evidence of a monosynaptic pathway between cells of the ventromedial medulla and the motoneuron pool of the thoracic spinal cord in rat: electron microscopic analysis of synaptic contacts. *Eur. J. Neurosci.,* 3, 55-65.

[515] Zagon, A., Terenzi, M.G., Roberts, M.FI.T. (1995) Direct projections from the anterior pretectal nucleus to the ventral medulla oblongata in rats. *Neurosci.,* 65, 253-272. Zemlan, F.P., Behbehani, M.M., Beckstead, R.M. (1984) Ascending and descending projections from nucleus reticularis magnocellularis and nucleus reticularis gigantocellularis: an autoradiographic and horseradish peroxidase study in the rat. *Brain Res.,* 292, 207-220.

[516] Zeng, S.L., Li, Y.Q., Rao, Z.R., Shi, J.W. (1991) Projections from serotonin- and substance P-like immunoreactive neurons in the midbrain periaqueductal gray onto the nucleus reticularis gigantocellularis pars a in the rat. *Neurosci. Lett.,* 131, 205-209. Zhuo, M., Gebhart, G.F. (1990) Spinal cholinergic and monoaminergic receptors mediate descending inhibition from the nuclei reticularis gigantocellularis and gigantocellularis pars alpha in the rat. *Brain Res.,* 535, 67-78.

[517] Zhuo, M., Gebhart, G.F. (1992) Characterization of descending facilitation and inhibition of spinal nociceptive transmission from the nuclei reticularis gigantocellularis and gigantocelluiaris pars alpha in the rat. *J. Neurophysiol,* 67, 1599-1614. Zhuo, M., Gebhart, G.F. (2002) Modulation of noxious and non-noxious spinal mechanical transmission from the rostral medial medulla in the rat. *J. Neurophysiol,* 88, 2928-2941. Zhuo, M., Gebhart, G.F. (2002) Facilitation and attenuation of a visceral nociceptive reflex from the rostroventral medulla in the rat. *Gastroenterol,* 122, 1007-1019.

[518] Zuckermann, E.G., Glaser, G.H. (1972) Urea-induced myoclonic seizures. An experimental study of site of action and mechanism. *Arch Neurol,* 27, 14-28.

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